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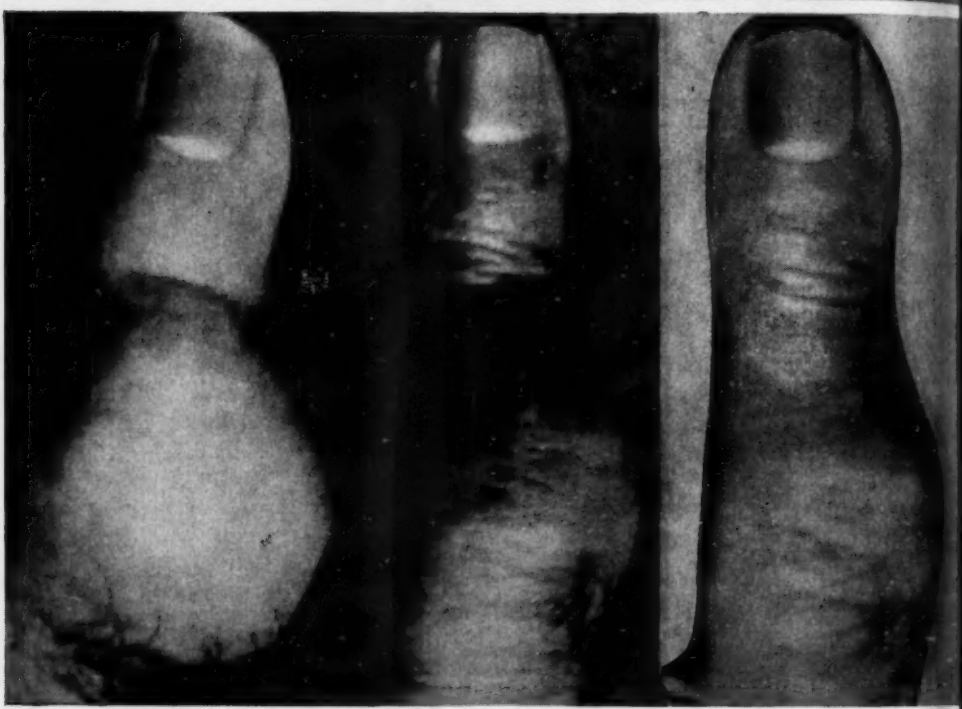

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STUDIES ON THE PATHOGENESIS OF FEVER

III. Failure to Demonstrate Fever-Producing Substances in the Tissues of Leukopenic Rabbits*

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In previously reported studies (1, 2), it was shown that normal rabbits react with characteristic fevers after injection of extracts of acutely inflamed rabbit tissues, of suspensions or extracts of rabbit polymorphonuclear leukocytes, or of the fluid portion of saline-induced peritoneal and pleural exudates. The ability of each of these materials to induce fever is retained after dialysis but is lost after heating at 90°C. for 30 minutes, suggesting a common component, but by no means ruling out the presence of similar rather than identical thermogenic substances. The fact that polymorphonuclear leukocytes are particularly rich in heat-labile pyrogen coupled with the presence of these cells in large numbers at acute inflammatory sites might also be taken as evidence of the identity of these fever-producing substances and of the granulocyte as the common source. However, experiments in granulocytopenic animals showed the presence of a similar fever-producing substance in sterile peritoneal exudates containing no granulocytes, indicating that under these conditions, at least, there must be some other source of endogenous pyrogenic material (2). Although an extensive survey of normal rabbit tissues and cells had failed to reveal thermogenic properties in any but the polymorphonuclear leukocyte (1), it was thought that similar testing of the tissues of leukopenic animals might reveal another source of pyrogen. Such a survey of the effects of extracts and suspensions of tissues obtained from granulocytopenic rabbits upon body temperature of normal animals has now been completed and the results form the basis of this report.

MATERIALS AND METHODS

Animals. Male rabbits of mixed breed and color weighing 2 to 3 kilos were obtained from a single commercial source. They were housed in air-conditioned rooms throughout the study. Rider's Laboratory Pellets containing no antibiotics were fed *ad libitum*; supplementary vegetables were not given.

Production of Leukopenia. Animals were made granulocytopenic by administration of nitrogen mustard (mechlorethamine HCl, Merck, hereafter referred to as "HN_2"). A single dose of 5.0 mgm. dissolved in 5.0 ml. of 0.85 per cent NaCl solution (hereafter referred to as "physiologic saline") was injected into a marginal ear vein. Total and differential leukocyte

* This study was supported by Grant A-660 of the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

counts of peripheral blood were carried out prior to injection of HN_2 and daily thereafter until leukocytes were reduced to less than 300/mm.^{3} or until the white cell count began to increase again. Approximately 20 per cent of animals died within 3 days after injection of HN_2 and in more than 30 per cent of those surviving, the leukopenia which ensued did not reach a point as low as 300/mm.^{3}; these animals were allowed to recover and were not used in the present study.

Preparation of tissue extracts. Extracts and suspensions were prepared from adrenals, bone marrow, brain, heart, kidney, liver, lung, lymph nodes, skeletal muscle, pancreas, skin, spleen, and testis. All tissues were excised from animals immediately after sacrifice by exsanguination in a cold room at 2–4°C. Specimens were weighed in chilled Petri dishes and extracts or suspensions were made by grinding in physiologic saline with or without centrifugation to remove particulate matter. Tissues were ground by one of several methods:

(a) A weighed aliquot of tissue was placed in a small Waring Blendor cup with 10 ml. of physiologic saline, containing no antibiotics, and the Blendor was run for 5 minutes in the cold room at 2–4°C. The homogenate was decanted into a 40 ml. centrifuge tube and stored at 4°C. (suspension) or centrifuged at 2000 R.P.M. for 30 minutes and the supernatant fluid stored (extract).

(b) A weighed aliquot of tissue was forced through a monel metal sieve, the mesh of which contained 289 openings/cm.^{2}, into a porcelain mortar. After addition of 2.0 ml. of physiologic saline/gm. of tissue, the mixture was ground with a motor-driven porcelain pestle until a smooth suspension was obtained (10–20 minutes). The tissue suspension was decanted into a 40 ml. centrifuge tube containing glass beads and shaken mechanically for 2 hours at room temperature. The entire suspension or the supernatant fluid obtained after centrifugation at 2000 R.P.M. for 30 minutes was stored at 4°C.

(c) A weighed aliquot of tissue was ground by hand in a TenBroeck apparatus after addition of 5–10 ml. of physiologic saline. Tissue suspensions or extracts obtained by centrifugation were stored at 4°C.

(d) Tissues were ground as in Method (c) using a motor-driven Teflon pestle in a fitted glass tube (3).

All tests were carried out within 4 days after preparation of tissue extracts or suspensions.

Testing of samples. Extracts were tested by intravenous injection into normal rabbits of amounts representing 1.0 to 5.0 gm. of tissue. Suspensions were tested by intravenous, intramuscular and intraperitoneal injection in normal rabbits. The amounts of each suspension injected into test animals were the equivalent of one whole organ for adrenal, pancreas, spleen, and testis, one-half an organ for heart, kidney, and lung, 15 grams of brain, liver and skeletal muscle, and 1 gram of bone marrow or lymph node.

As in the previous study, sudden death occurred in several rabbits given tissue preparations by the intravenous route, presumably due to thromboplastic activity. This was prevented in most instances by premedication of test animals with 50 mgm. of heparin intravenously 30 minutes before injection combined with "desensitization" by injection of 0.1 or 0.2 ml. of the test material 20 minutes before the total volume was injected, as recommended by Thomas (4).

Temperature Records. Rectal temperatures were recorded in all tests for fever. When extracts or suspensions were injected intravenously, animals were placed in metal stalls, secured by loose-fitting collars, and temperatures were taken at intervals of 30 minutes for 6 hours, using resistance coils which remained in the rectum throughout the test period and an automatic recording device (the Foxboro Rabbit Scanner and Fever Recorder). In all cases, periods of acclimatization to the stalls preceded actual tests and an adequate number of baseline recordings was obtained before any injection was carried out. In experi-

ments involving injection by other routes, animals remained free in their cages and temperatures were recorded hourly for 24 hours using ordinary clinical thermometers.

Avoidance of Bacterial Pyrogens. Rigid precautions against bacterial pyrogen contamination were observed. These have been described in detail elsewhere (1). All tissue preparations were cultured in thioglycollate broth, incubated for 48 hours at room temperature and at 37°C. In instances of contamination, material was discarded. It should be mentioned that contamination by bacteria, particularly Gram negative bacilli, was found in about 20 per cent of the extracts. This is a considerably higher incidence than was observed in the

TABLE I

Saline Extracts of Tissues of Leukopenic Rabbits Tested by Intravenous Injection in Normal Rabbits

Tissue	Extracts Prepared		No. Test Animals†
	Method*	No.	
Adrenal	b	2	4
	c	3	6
	d	3	5
Bone marrow	c	4	7
	d	5	10
Brain	a	2	4
	c	2	3
	d	2	4
Heart	a	4	8
	b	4	8
Kidney	a	4	6
	c	5	10
	d	4	6
Liver	a	4	9
	b	3	9
	c	3	11
	d	4	7
Lung	a	4	8
	c	3	5
	d	3	7
Lymph node	a	2	4
	b	4	6
	c	3	6
	d	3	5
Pancreas	c	2	4
	d	2	4
Skin	b	7	11
Spleen	a	5	10
	b	4	8
	c	4	8
	d	4	8
Testis	b	2	4
	c	2	3
	d	2	6

* See text for details of preparation.

† None of the test animals reacted to injection of tissue extracts with fever.

TABLE II

Suspensions of Tissues Obtained from Leukopenic Rabbits Tested by Injection in Normal Rabbits

Tissue	Suspensions Prepared		No. of Test Animals and Route of Injection†		
	Method*	No.	I.V.	I.P.	I.M.
Adrenal	c	3	3	3	3
	d	3	3	3	3
Bone Marrow	d	5	4	5	5
Brain	c	3	3	3	3
	d	4	4	3	4
Heart	a	3	3	3	3
	b	3	3	3	3
Kidney	a	5	5	5	5
	d	7	4	4	5
Liver	a	4	4	4	4
	b	2	4	4	4
	d	4	4	4	4
Lung	d	5	4	5	8
Lymph node	a	6	3	2	4
	b	5	5	4	4
	c	4	4	4	4
	d	4	4	4	4
Pancreas	c	2	2	2	4
	d	2	4	3	4
Skin	b	8	4	4	4
Spleen	a	2	4	4	4
	c	6	3	7	4
	d	6	3	7	6
Testis	c	4	4	4	4
	d	4	4	4	4

* See text for details of preparation.

† None of the test animals reacted to injection of tissue suspensions with fever.

previous study in which tissues of normal rabbits were used (1) and is probably related to the occurrence of spontaneous infections in animals given HN_2 (5).

RESULTS

The extracts and suspensions prepared and tested by injection into normal rabbits are shown in Tables I and II. None of the preparations produced any consistent alteration in the body temperature of test animals.

DISCUSSION

A previous study of tissues and cells obtained from normal rabbits revealed pyrogenic activity only in polymorphonuclear leukocytes. However, the finding of a similar fever-producing substance in granulocyte-free peritoneal exudates obtained from rabbits with HN_2-induced leukopenia indicated that, under these conditions, other tissues might act as a source of endogenous pyrogenic ma-

terial. The failure to find such substances in tissues of leukopenic rabbits by the relatively crude methods of the present study does not constitute a conclusive argument against this concept and several possible explanations can be offered. It is conceivable that the tissues tested might, in greater amounts or after irritation and injury, produce pyrogenic substances. Furthermore, as was the case with normal rabbits (1), certain cell types could not be tested in quantity, an obvious omission being vascular endothelium. Atkins and Wood (6) have reported finding an "endogenous pyrogen" in the blood of rabbits after injection of bacterial endotoxin. These authors believe that this substance may mediate the febrile response to endotoxin and have given good reasons for thinking that a portion of it originates from leukocytes damaged by the endotoxin. If this is the case, the fact that granulocytopenic rabbits react to endotoxin injection with fevers comparable to those of normal animals (7) is best explained by assuming that other tissues, under proper conditions, can serve as a source of endogenous fever-producing substances. The presence of "endogenous pyrogen" in the blood of granulocytopenic rabbits given endotoxin has not been demonstrated although studies to this end are underway in this laboratory. Recently completed experiments indicate that the fevers accompanying pneumococcal infection and hypersensitivity reactions in rabbits are also mediated by similar thermogenic substances of tissue origin (8) although conclusive proof of granulocytic origin of these endogenous pyrogens is still lacking.

Finally, it might be pointed out that granulocytes are not entirely absent in animals given HN_2, and it is possible that such animals still possess enough of these cells to account for febrile reactions. However, quantitative data available from prior studies (1) indicate that approximately 400 million granulocytes are needed to elicit a brief febrile response, and this number of granulocytes far exceeds that present in the circulation of HN_2 treated animals that are still able to respond to various stimuli with prolonged fevers.

SUMMARY

The effect of extracts and suspensions of tissues obtained from granulocytopenic rabbits upon body temperature was tested by injection into normal animals. No evidence of thermogenic substances was found in any of the materials tested. The relationship of these findings to previous descriptions of "endogenous" tissue pyrogens is discussed.

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STUDIES ON THE PATHOGENESIS OF FEVER

IV. Further Observations on the Production of Fever in Rabbits by the Fluid of Sterile Exudates*

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The fluid portion of sterile exudates produced by infusing 0.85% NaCl solution into the peritoneal cavity of rabbits contains a heat-labile fever-producing substance (1, 2). The properties of this thermogenic material differ in several respects from those of ordinary bacterial pyrogens and resemble closely those of a fever-producing substance that can be extracted from polymorphonuclear leukocytes. It has not yet been demonstrated conclusively that the pyrogenic materials in exudates and in leukocytes are identical.

The finding of such substances, presumably of endogenous origin, is of considerable interest in relation to the hypothesis that the febrile response accompanying various types of disease is due to products of tissue injury. However, it remains to be determined whether materials present in exudates or injured tissue that are capable of causing fever when injected into normal recipient animals actually bear any relationship to the occurrence of febrile responses in the "host" or donor animals. The present report summarizes experiments designed to examine the role of "endogenous pyrogen" in animals with saline-induced peritoneal inflammations.

MATERIALS AND METHODS

General. Animals and their care, procedures for recording temperatures, and precautions against contamination of materials by bacterial pyrogens were the same as in previous studies (1–3).

Production of Exudates. Animals were tied on their backs, their abdomens were shaved, and 300 ml. of 0.85 per cent NaCl. solution (hereafter referred to as "physiologic saline") containing no antibiotics was injected through an 18 gauge needle into the peritoneal cavity. Standard Fenwal apparatus was employed and the drip was regulated so that the infusion was completed in 3–3½ hours. Animals were maintained in the recumbent position for 3–4 hours after termination of the infusion. Under nembutal anesthesia, the abdomen was opened through a midline incision and all fluid remaining in the peritoneal cavity was aspirated into a 250 ml. centrifuge bottle. Total and differential leukocyte counts were performed, samples of exudate were cultured in thioglycollate broth incubated at room temperature and at 37°C., and after centrifugation at 2000 R.P.M. for 20 minutes, supernatant fluids were decanted and stored at 4°C. This procedure differed only slightly from

* This study was supported by Grant A-660 of the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

that used in an earlier study and the characteristics of the exudates obtained in this way were similar to those previously described in detail (1, 2). Each exudate was tested by intravenous injection of 10 ml. portions into two normal rabbits. When febrile responses occurred, 10 ml. samples of the material were retested after heating at 90°C. for 30 minutes, a procedure which destroys the endogenous pyrogen in exudates but leaves any contaminating bacterial pyrogen unimpaired in its ability to produce fever.

Collection of Blood and Lymph. In several experiments, animals were bled aseptically by cardiac puncture through 18 gauge needles. Blood was allowed to clot at room temperature and serum was separated by centrifugation at 2000 R.P.M. for 30 minutes. Sterility was tested by culture in thioglycollate broth. Serum was stored at 4°C. until tested in animals.

Thoracic duct lymph was collected by a procedure similar to that used by Schulz *et al.* (4). Under nembutal anesthesia, an incision was made in the left anterior cervical region exposing the junction of the jugular and subclavian veins to form the left superior vena cava, and the subclavian was ligated about 0.5 cm. above this point. The jugular was dissected out distally, all tributaries were carefully ligated and the main vessel was ligated 2.5–3.0 cm. above the first rib. The left superior vena cava was clamped just below its origin, leaving an isolated venous pouch into which the entire lymphatic flow of the thoracic duct drained. Cannulation of the jugular venous segment was easily carried out, using polyethylene tubing, and lymph was collected in 40 ml. centrifuge tubes containing heparin. Collecting tubes were changed at intervals of 10–30 minutes. Total and differential leukocyte counts and cultures in thioglycollate were performed on each sample. In normal animals, gentle massage of the abdomen was usually required to initiate or to maintain a flow of lymph; this was less often the case in animals given intraperitoneal infusions. The injection of Evans blue dye into the peritoneum was regularly followed by staining of collected lymph within 1 to 3 minutes. Occasional specimens contained large numbers of erythrocytes but the incidence of this tended to decrease throughout the collection periods and was probably due to undetected capillary drainage into the venous segment. Vigorous abdominal massage almost invariably resulted in the appearance of gross blood in the lymph, possibly a result of stimulation of hepatic lymphatic drainage (5). Lymph was stored at 4°C. until tested in animals.

EXPERIMENTAL RESULTS

Body Temperature of Rabbits During Production of Peritoneal Exudates. In order to determine whether or not pyrogenic material is absorbed systemically from sterile inflammatory exudates in the peritoneal cavity in quantities sufficient to cause fever, the following experiments were done.

1. Twelve normal rabbits were tied on their backs, and rectal temperatures were recorded at intervals of 15 minutes for two hours to obtain a baseline. Each of six animals then received an intraperitoneal infusion of physiologic saline, the others serving as controls. Temperatures were recorded at intervals of 30 minutes throughout the infusion period (approximately three hours) and for eight hours thereafter. The six experimental animals were then sacrificed and peritoneal fluids were collected. Although each of the exudates collected was shown by testing in normal recipients to contain heat-labile pyrogenic material, no elevation of rectal temperature was found in any of the six "donor" animals or the controls during the period of exudate accumulation. This experiment was repeated with another group of ten rabbits (four controls, six given infusions) with the same results.

2. Because of peculiar difficulty in eliciting a febrile response in a rabbit restrained in the recumbent position (6), eight rabbits were given intraperitoneal saline infusions as above,

but were released and returned to their cages at the conclusion of the injections. Rectal temperatures recorded at intervals of 30 minutes for the succeeding eight hours again failed to show any consistent alterations as a result of peritoneal exudation. Due to technical difficulties, peritoneal exudates were collected and injected into normal recipients from only six of these eight rabbits, but in each of these the presence of heat-labile pyrogen was confirmed.

3. Although the introduction of physiologic saline solution into the peritoneal cavity by slow infusion generally yields better results in terms of quality of exudate obtained, rapid injection by syringe and needle is also effective. Six normal rabbits were given 300 ml. of physiologic saline intraperitoneally within 10 minutes and their temperatures were recorded hourly for 12 hours during which time they were unrestrained. No fevers resulted. Fluid aspirated from the peritoneal cavity of each animal at the sixth hour was tested in normal recipients by intravenous injection and shown to be pyrogenic. These six rabbits were then given 300 ml. of physiologic saline intraperitoneally three times weekly for six weeks, their temperatures being recorded four times daily throughout this period. Aspirated peritoneal fluids consistently showed striking polymorphonuclear leukocytosis and produced fevers in test animals. However, there was no evidence during this period of any febrile reaction in the "donor" animals. Another experiment in a group of four animals given 250 ml. of physiologic saline intraperitoneally on alternate days for 24 days resulted in no fevers.

From these observations it was concluded that absorption of the heat-labile pyrogenic material present in saline-induced peritoneal exudates is insufficient to produce a febrile response in the "host" rabbit.

Tests of Serum for Presence of Tissue Pyrogen. Although febrile responses were not observed in rabbits developing peritoneal exudates after infusions of physiologic saline, further attempts to demonstrate systemic absorption of fever producing material were carried out by testing serum for its presence.

Thirty-one rabbits were given infusions of physiologic saline intraperitoneally. At various times up to 12 hours after saline injection was discontinued, they were bled by cardiac puncture, as much blood as possible being collected from each animal. Serum was separated, pooled by collection times, and tested by intravenous injection of 50 ml. quantities into normal animals. Table I details the time intervals of collection, the quantities tested, and the number of test animals. None of the test animals showed febrile responses to serum collected from animals with saline-induced peritoneal exudates.

TABLE I

Serum Collected from Rabbits with Saline-Induced Peritoneal Exudates and Tested by Intravenous Injection in Normal Rabbits

Hr. after NaCl. Infusion	No. animals bled	No. test animals*
2	6	6
4	5	5
6	4	5
8	6	6†
10	5	4
12	5	5

* Dosage of serum was 50 ml. i.v.; none of the test animals had fever.

† One animal received only 30 ml. of serum.

TABLE II

Serum Collected from Rabbits After Injection of Peritoneal Exudate and Tested by Intravenous Injection in Normal Rabbits

Minutes after injection of exudate	No. animals bled	No. test animals*
5	3	3
10	3	2
15	3	2
20	3	3

* Dosage of serum was 40 ml. i.v.; none of the test animals had fever.

These results were interpreted as further evidence against significant absorption of fever-producing material from the peritoneal cavity. However, the following experiment in which normal animals were bled after injection of exudate indicates that this method may be relatively insensitive in detecting the presence of small amounts of endogenous pyrogen.

Each of 12 normal rabbits was given 20 ml. of pooled peritoneal fluid intravenously. (It had been shown previously that 5.0 ml. of this pooled fluid was regularly capable of producing fever in normal rabbits.) Groups of three animals were bled by cardiac puncture 5 minutes, 10 minutes, 15 minutes, and 20 minutes after injection. Pooled serum was tested in 40 ml. quantities in normal rabbits (Table II). None of the recipient animals responded with fever, indicating a rapid removal or inactivation of the injected pyrogenic material. It was demonstrated in a previous study that admixture with plasma *per se* does not influence the ability of peritoneal fluids to cause fever (2).

Tests of Thoracic Duct Lymph for Presence of Tissue Pyrogen. Because of the probability that any absorption of material from the peritoneal cavity would take place through the lymphatic system, thoracic duct lymph was collected from animals with saline-induced peritoneal exudates and tested for the presence of fever-producing material.

Thoracic duct lymph was collected from 18 normal rabbits, the periods of collection varying from 30 minutes to 3½ hours and the total quantities from 11 ml. to 33 ml. Each sample was tested by intravenous injection into a normal rabbit; no fevers resulted, indication that normal lymph is nonpyrogenic. Leukocyte counts of normal lymph ranged from 17,000 to 83,000 cells/mm.^{3} and examination of stained smears showed that the cells were

TABLE III

Thoracic Duct Lymph Collected from Rabbits with Saline-Induced Peritoneal Exudates and Tested by Intravenous Injection in Normal Rabbits

Hr. after NaCl. Infusion	No. donor animals	No. test animals*
4	18	21
8	20	40

* The dosage of lymph ranged from 9.0 to 38.0 ml.; no more than two specimens were obtained from a single animal and none of the test animals had fever.

invariably lymphocytes. By means of total and differential leukocyte counts, it was therefore possible to ascertain the presence of adequate amounts of lymph even in the presence of considerable contamination by blood in the collection tubes.

In similar fashion, thoracic duct lymph was collected from rabbits that had been given physiologic saline intraperitoneally. Collection periods varied from 20 minutes to 1½ hours and collections were begun 4 hours or 8 hours after termination of the intraperitoneal infusion. In every instance, when collection of lymph was stopped, animals were sacrificed and peritoneal fluids were collected to be tested for the presence of fever-producing material. A total of 61 samples of lymph, ranging in volume from 9.0 to 38.0 ml. which were obtained from 38 rabbits with pyrogenic peritoneal exudates, were tested by intravenous injection into normal rabbits (Table III). None caused any rise in rectal temperature.

Because no fever followed injection of thoracic duct lymph in volumes greater than the amounts of peritoneal exudate needed to cause brisk fevers in the donor animals, it was again concluded that absorption of endogenous pyrogen from the peritoneal exudate occurred in amounts insufficient to elicit febrile responses in the host.

Finally, five normal rabbits were anesthetized with nembutal, cannulation of the isolated jugular vein was carried out and lymph was collected for 45 minutes. At this time, collection tubes were changed and each animal was given an intraperitoneal injection of 50 micrograms of purified *Shigella flexneri* endotoxin (obtained from Dr. L. E. Cluff) in 10 ml. of physiologic saline. Collection of lymph was continued for 10 minutes after injection of this potent bacterial pyrogen. The pre- and post-injection lymph samples from each animal were then tested by injection into normal recipients. None of the control specimens was pyrogenic; in contrast, test animals given the lymph collected after injection of endotoxin reacted with high fevers for several hours, indication of absorption of this exogenous pyrogen via the lymphatics.

Total and differential leukocyte counts performed on lymph samples collected from animals with saline-induced peritoneal exudates or from animals given bacterial endotoxin again revealed lymphocytes without polymorphonuclear cells, and no change in the total cell counts.

DISCUSSION

The fluid portion of sterile peritoneal exudates in rabbits contains a heat-labile fever-producing substance, and a similar pyrogenic material is demonstrable in extracts of rabbit polymorphonuclear leukocytes (1, 2). The present study has shown that animals with such exudates are not febrile and that the endogenous pyrogen in peritoneal exudates is not present in serum or thoracic duct lymph in detectable quantities. These findings, of course, raise a serious question as to the role of such endogenous pyrogens in the production of fever in the host animal. However, the peritoneal inflammation produced by saline is relatively mild and recently completed studies (7) indicate that significant absorption of tissue pyrogen can occur from sites of more intense inflammation and that this absorption is accompanied by fever. The failure of peritoneal exudation after saline injection to produce fever is therefore probably best

explained on the basis of the relatively mild reaction elicited by this irritant and cannot be taken as conclusive evidence against an important role of products of tissue injury in the pathogenesis of feer.

SUMMARY

Although saline-induced peritoneal exudates contain a heat-labile fever-producing substance, significant systemic absorption of endogenous pyrogenic material from the inflammatory site could not be demonstrated in animals with exudates. Rabbits given saline intraperitoneally remained afebrile and both serum and thoracic duct lymph from such animals were non-pyrogenic for normal rabbits, although the injection of peritoneal fluid regularly elicited fever in normal rabbits. The relationship of these findings to the hypothesis that fever is caused by products of tissue injury is discussed.

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CARCINOID CARDIOVASCULAR DISEASE

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In the last few years there has been much comment in the British medical literature about a syndrome given the name of Baron von Münchausen (3) because the affected persons have travelled widely from hospital to hospital and tell dramatic tales of symptoms which are purely fictitious. The syndrome under discussion here might be given the name of Jules Verne, for its component manifestations are, at first thought, so fantastically diverse as to test the credulity of the most hardened clinician; yet the passage of time and accumulation of experience have demonstrated fact stranger than fiction. The Jules Verne of this piece is Pierre Masson, who forty years ago insisted on the endocrine function of the enterochromaffin cells and referred to the carcinoid tumors derived from these cells as endocrine tumors (37). As with science and Jules Verne, the nosography of the syndrome associated with carcinoid tumors, particularly with respect to the striking valvulitis of inflammatory type, has far outstripped the speculations of Masson, which originally seemed so wild.

Beginning in 1930 there appeared at least six individual case reports of pulmonary stenosis and malignant carcinoid (11) (71) (12) (13) (56) (35) (18). Most of the authors considered the pulmonary stenosis rheumatic (56) or even congenital (18), and none thought the association more than coincidence. However, about 1953, three groups independently reported on a true syndromal relationship: Isler and Hedinger (46) in Zurich; Thorson, Biörck, Walderström and others (83) in Sweden; and Rosenbaum, Santer and Claudon (69) in Milwaukee. Furthermore, these observers delineated two other vascular components in addition to the right-sided valvular lesions: 1) a particular type of telangiectasia and 2) episodic cutaneous vasomotor phenomena, mainly flushing and mobile cyanosis. Hyperperistalsis and broncho-constriction were also described. The presence of hepatic metastases of the carcinoid was a constant feature.

Hitherto, there was accumulated a considerable body of information concerning the biology of certain material produced by enterochromaffin (argentaffin) cells of the intestine, the parent cell of the carcinoid tumor. Erspamer and his collaborators in Bari, Italy, the principal investigators in this field, succeeded in isolating from gastrointestinal mucosa a material which produced contraction of smooth muscle (24). They subsequently identified this material, called by them "enteramine", as 5-hydroxytryptamine (25). (See also refer-

FIG. 1. Case of Sir Maurice Cassidy (11), probably the first reported. The flushing and the telangiectases in the butterfly area of the face are well shown. The original, in color, demonstrates well patchy cyanosis over the upper part of the chest. (Reproduced with the permission of the Royal Society of Medicine, London.)

ence no. 19.) Barter and Pearse (4) demonstrated that granules of enterochromaffin cells are a complex of enteramine with the formalin of the fixative.

Meanwhile, several groups were making seemingly unrelated observations on the serum vasoconstrictor factor which was discovered many years ago (80)

(47) and more recently was termed "serotonin" by Page and his co-worker (58). (Because of the intimate relation of the serum vasoconstrictor "factor" ("principle" or "substance") to the blood platelets, the terms "thrombocytin" (68) and "thrombotonin" were also applied to the material.) The pharmacology of this agent was explored in animals (66) (68) (67) (52) (31) and in man (15) (60) (17). With intravenous administration in man its effects on systemic arterial blood pressure were variable. It did, however, appear to produce pulmonary hypertension in man. The *in vitro* effects of serotonin on smooth muscle were identical to those of enteramine, and serotonin was likewise identified as 5-hydroxytryptamine (64).

In the discussion here the convention adopted in most recent publications on the subject (24) will be followed: 5-hydroxytryptamine (5-HT) will be the term employed.

The normal enterochromaffin cells of the gastrointestinal mucosa are believed to constitute a "diffuse endocrine gland", to manufacture 5-HT from the amino acid tryptophane, and to release this substance into the lymph and/or blood. In the blood 5-HT seems to be selectively adsorbed by the platelets (45) which become circulating reservoirs. In passing it is of interest to note that platelets adsorb other vasoactive amines: histamine (45), adrenaline and noradrenaline (89). Amine oxidase is mainly responsible for the inactivation of 5-HT. The main breakdown product is 5-hydroxyindole-acetic acid (5-HIAA), a normal constituent of human urine.

Several hypotheses (24) for the physiologic role of 5-HT have been advanced: 1) that it is a factor in hemostasis (by production of vasoconstriction); 2) that it contributes to the control of vascular tone and therefore of arterial blood pressure; 3) that it participates in the regulation of renal function; and 4) that it plays a role in the normal function of the central nervous system. The localization of argentaffine cells in the gastrointestinal mucosa and the fact that these cells at times demonstrate intimate relationships with the nerves of the plexus of Meissner (54) suggest a fifth physiological role of 5-HT; 5) regulation of normal intestinal tone. In fact, however, the physiological role of 5-HT has not been established with complete certainty.

As far as pathological implications are concerned, in only two conditions (other than carcinoid) has an alteration in circulating 5-HT been identified; in thrombocytopenia the values may be very low (7), in cirrhosis moderately low (24). In hypertension no abnormality was discovered. Comroe (14) has suggested that 5-HT may play a role in the pathological physiology of pulmonary embolism and by inference possibly that of other arterial embolism, coronary thrombosis, and phlebothrombosis. Woolley and Shaw (91) have suggested that schizophrenia and other mental disorders may be due to abnormal concentrations of 5-HT in the central nervous system.

The Swedish group (83) suggested that 5-HT may play a role in the patho-

genesis of the cardiovascular manifestations associated with malignant carcinoid. The suggestion has found support from several observations. In 1924 Danisch (20) discovered pharmacodynamic properties like those of adrenaline in extracts of a carcinoid of the appendix. In 1925 Forbus (28) described and illustrated a case of argentaffine tumor in which crystals were seen in the histological sections. Forbus speculated that "the crystals may represent a substance elaborated by the cells of tumor". In 1936 Feyrter and Unna (27) and in 1941 Selberg (72) reported on the occurrence of pressor material in carcinoid tumors. Lembeck (49) (50) more recently demonstrated substantial amounts of 5-HT in carcinoid metastases and Ratzenhofer and he (65) also demonstrated it in a non-metastasizing carcinoid of the appendix. Other workers demonstrated it, or at least material with similar chemical and pharmacodynamic properties, in blood (62) of patients with metastatic carcinoid. The work of Erspamer (23) and of Udenfriend and co-workers (84) (85) indicated that in man a large portion of 5-HT is excreted in the urine as 5-hydroxyindole-acetic acid (5-HIAA). These observations suggested (21) the usefulness of the relatively simple colorimetric determination of the latter substance as a diagnostic test for carcinoid. Possibly carcinoid without metastases might result in the presence of increased amounts of this material in the urine. Page and co-workers (59) have reported that indeed very large amounts of 5-HIAA are excreted in patients with metastatic carcinoid tumors and that the test appears to be specific.

REPORT OF CASES

The first case is described in detail because it illustrates typical clinical features of metastasizing carcinoid, namely, diarrhea, asthma, and flushing attacks. Congestive heart failure developed one month before death. The diagnosis of carcinoid was established at laparotomy by biopsy of one of the many metastatic masses in the liver. Because autopsy information is not available the exact nature of the cardiovascular lesion responsible for heart failure is unknown.

Case 1. J. B. (J.H.H. 383666)*, born in 1893, was a white college dean seen at this hospital in 1946. The patient had had diarrhea for 18 months and a weight loss of 30 pounds in the 6 or 8 months previously. "A lesser complaint was flushing of the face and neck, which had started two years previously." The flushing was not related to the diarrhea. He developed attacks of asthmatic breathing which were unrelated to exertion and not associated with flushing.

Physical examination revealed a weight of 170 pounds when dressed. The face was flushed with fine telangiectases. The blood pressure varied from 170/82 to 220/116 mm. Hg being usually at the higher figure. Following massage of the liver the pressure fell to

* Dr. John Tilden Howard studied this patient and Dr. Alfred Blalock performed laparotomy.

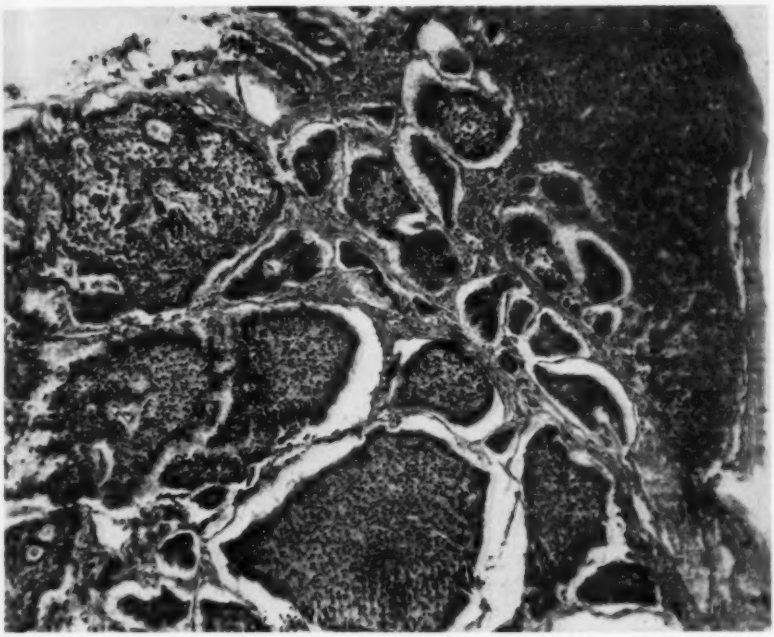

FIG. 2. Liver metastasis in Case 1. ×100.

142/78 gradually returning to 170 mm. systolic without objective flushing. There were a few asthmatic wheezes in the lungs but no abnormal cardiac findings. The liver and spleen were both enlarged.

The hemoglobin was 80% of normal, white cell count 12,700 per cu. mm. Total bilirubin was 1.6 mgm.%. An EKG revealed "definite evidence of trouble in the coronary system." Barium enema showed evidence of striking irritability of the colon. The stomach on GI fluoroscopy showed pylorospasm and hyperperistalsis. X-ray of the chest showed a little pleural thickening at the right lung base and mild limitation in the excursion of the right half of the diaphragm.

Laparotomy was performed on April 30, 1946. The gallbladder was enlarged, contained many stones, and was removed. The liver contained many tumor masses which were histologically typical of argentaffine tumor (Fig. 2). No abnormality of the entire intestinal tract, including the appendix, could be detected.

The comment of the surgeon was that "he has a peculiar peripheral circulation system." Postoperatively it was noted that the patient was "sweating a lot and looks very red but this is hard to evaluate because of unstable sympathetic system." Postoperatively he complained of much rectal pain and an abscess broke and drained spontaneously inside the rectum.

The patient remained reasonably well, although flushing, asthma, and diarrhea continued for four months when manifestations of congestive heart failure set in. Death occurred 5½ months after laparotomy.

Among the last 15,000 autopsies at The Johns Hopkins Hospital nine cases of metastasizing carcinoid occurred. (Isler and Hedinger (46) in Zurich found five such cases among 16,812 autopsies. Spain (77) found ten cases among 8,000 autopsies in adults; in one of the ten only lymph nodes were involved.) In one of these (Case 2 below) advanced cardiovascular changes were discovered. Compared with the previously reported cases it demonstrates a set of circumstances peculiar to it, a set of circumstances which may assist elucidation of the pathogenesis of the valvulitis.

Case 2.* This was a sixty-eight year old white unmarried female shop worker who was referred to this hospital because of "trouble breathing" for one year.

The patient had been very well prior to the present illness. A "fibroid of the womb" had been present for about thirty years. One year previously, vaginal bleeding was noted. Dilatation and curettage was performed in another hospital, and the patient was told no abnormality was found. There was no further bleeding thereafter.

About one year before admission she noted the insidious onset of marked weakness and of dyspnea on exertion. Progressive weight loss occurred to the extent of 30 to 40 pounds during the course of the year.

Two months before admission, she consulted a physician for the first time because of dizziness. A week later she was troubled by moderate diarrhea. She was found to have polycythemia (6.59 million r.b.c./mm^3) and leucocytosis (19,000 w.b.c./mm^3). The dyspnea was improved by phlebotomy, but the profound weakness continued. The veins were always difficult to enter.

One month before admission, barium enema, performed because of continuing diarrhea, showed only diverticulosis of the colon and what was interpreted as calcification of uterine fibroids. The heart was found to be greatly enlarged but the lung fields were clear. The blood pressure fell gradually from 170/90 to 130/70 mm. Hg. There was no fever. It might be noted at this point that subsequent inquiries have revealed that the patient (quoting from a sister's letter) had "for some time had flushing attacks during which her face would get very red. These attacks were always obvious to those around her and were also noticed by her nurse in the hospital here before transfer to your hospital."

On admission to this hospital the patient was weak and wasted. She was moderately orthopneic and promptly became dyspneic and cyanotic when removed from an oxygen tent. The patient presented a most dramatic appearance. Each malar eminence was covered by a peculiar telangiectatic, erythematous area against a background of more generalized violaceous erythema. Fingers, toes and mucous membranes were cyanotic. The retinal vessels were dilated and tortuous. The neck veins were markedly engorged, but peripheral veins were paradoxically small. The lungs were remarkably clear. The heart rate was 120 per minute. A systolic lifting impulse was present to the left of the sternum. A grade IV systolic murmur was loudest at the left mid-precordium in the fourth interspace. A diastolic murmur, creating a to-and-fro complex, was heard in the same area and was loudest when the patient was in the left lateral decubitus position. The liver was little enlarged and was nontender. There was no splenomegaly or ascites. A knobby mass of rocky consistency extended up from the pelvis to the level of the umbilicus. There was no significant peripheral edema.

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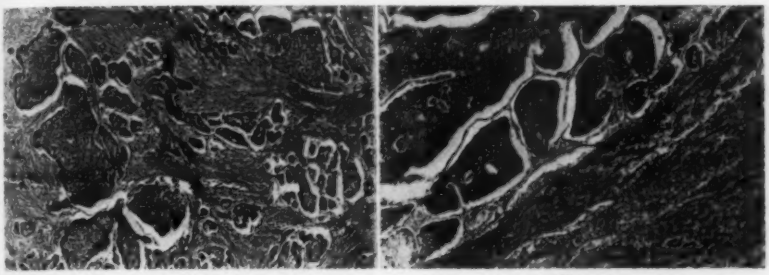
* For many clinical details I am indebted to Dr. P. A. Tumulty and Dr. A. M. Harvey, who cared for the patient in her final hospital admission, and Dr. J. Wesley Plowman of Harrisburg, Pennsylvania, the referring physician.



A B

FIG. 3. The carcinoid tumor (Case 2). A. The ovarial metastasis. Whether the amount of connective tissue stroma is significant as indicating a specific sclerosing effect of the tumor is difficult to state since many other tumors demonstrate the same phenomenon. B. Metastasis in the liver.

Black cyanosis of the extremities, with feeble pulses and with some thickening of the ends of the digits, was very impressive.

The patient was critically ill during the three days in the hospital before her death. However, the blood pressure was 200/100 mm. Hg a few hours before death.

The red blood cell count was 6.54 million/mm^3 and the white count 10,800. Electrocardiogram showed left axis deviation, flat T_1 and delayed precordial transition.

All who saw the patient were much impressed by her dramatic appearance but were perplexed by the biazrre clinical picture. Most observers interpreted the auscultatory findings as indicating disease of both the aortic and the mitral valve. She was thought most likely to have rheumatic heart disease and possibly also obliterative pulmonary arterial disease.

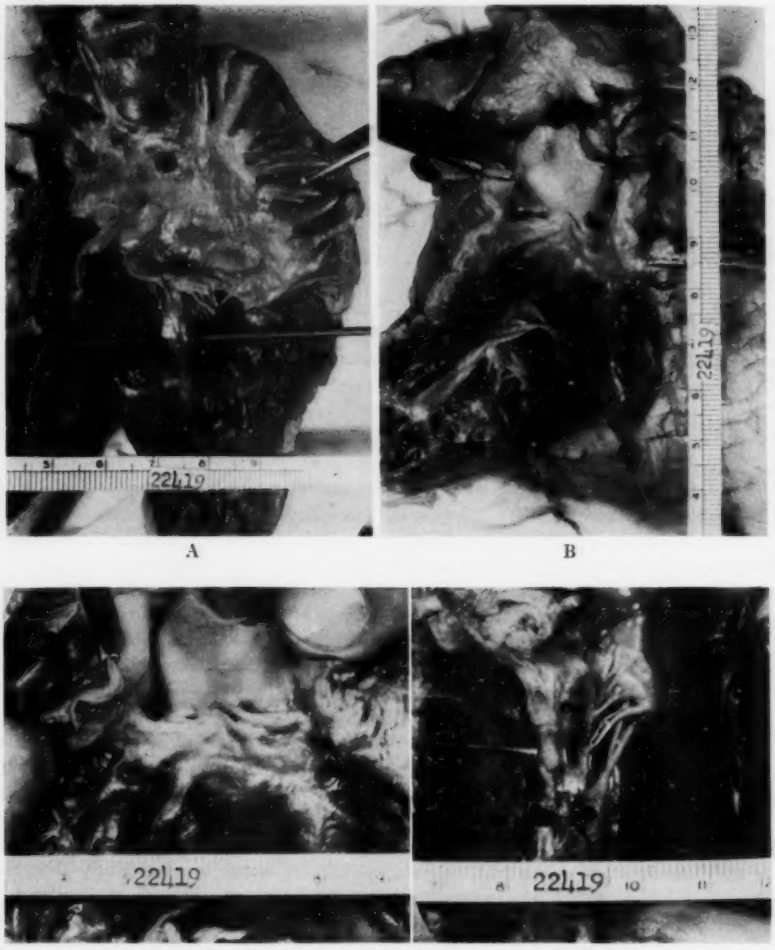
Autopsy (performed by Dr. Paul Griffith) revealed the following pertinent findings: There was no discrepancy in the circumferential measurements of the legs. The heart weighed 400 gms. A patency of the foramen ovale measured about 1.5 cm. in its maximum dimension and was covered by a lax fibrous membrane with several perforations. The margins of the tricuspid valve and its chordae tendineae were markedly thickened with false shortening of the latter so that the papillary muscles inserted virtually on the edge of the cusps (Fig. 4A). The valve appeared to be mildly stenotic as well as obviously regurgitant. The right atrial myocardium was hypertrophied. The pulmonary valve was extremely deformed (Figs. 4B and C). Its three cusps were thickened and retracted with the production of a structure which functionally must also have been both stenotic and regurgitant. A curious flap of muscle extended from the anterior wall of the right ventricle to insert below one of the pulmonary cusps. There was rather marked fibrosis of the mitral cusps and chordae tendineae (Fig. 4D) and mild change in one aortic cusp.

The smaller pulmonary arteries were filled with numerous red, laminated thrombi which were found in vessels with diameters as large as 0.5 cm. These thrombi in effect occluded almost all of the intrapulmonary arteries.

The liver weighed 1200 gms. In it were a metastatic nodule with a cystic center measuring 3 cm. in its greatest dimension and a few other nodules less than 1 cm. in size.

There were infarcts in the spleen. The orifices of the celiac and superior mesenteric arteries were completely occluded by laminated thrombus of presumed embolic origin.

The uterus was occupied by numerous fibrous nodules. The right ovary was greatly enlarged measuring 12 x 9 x 7 cm. The serosa was intact. On section it was solid yellow with a whorled fibrous pattern. The perivaginal and ovarian veins were dilated and thrombosed.



A B C D

FIG. 4. The gross appearance of the heart valves (Case 2). A. Tricuspid valve. Note also sclerosis of endocardium of right atrium. The perforation of the inter-atrial septum is shown. B. Outflow tract of right ventricle with scarred pulmonary valve above, scarred tricuspid valve below. C. Close-up of scarred pulmonary valve showing also the anomalous muscle bundle on the right. D. Scarred chordae tendineae of mitral valve.

The terminal 30 cm. of ileum was edematous and red-black in color. The mesenteric arteries supplying this area were occluded by thrombi. In the ileum just proximal to the ileocecal valve there was a firm, oval, smooth mass 3 x 1.5 x 1.0 cm. in size, projecting into the lumen of the bowel. On section the nodules were found to infiltrate the muscle in linear strands and formed an indurated mass at the insertion of the ileocolic ligament.

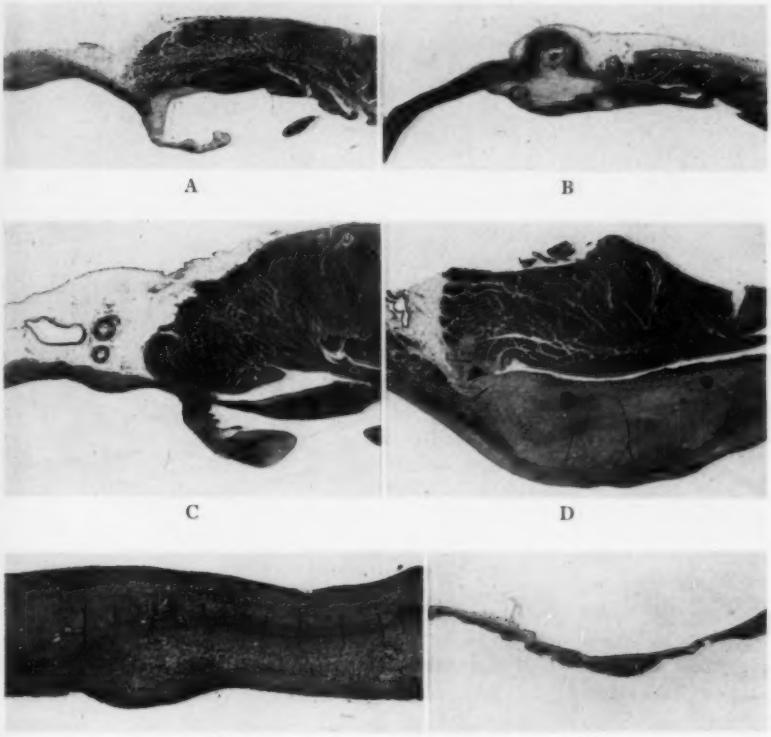


FIG. 5. Photomicrographs of the scarred valves (Case 2). A. Tricuspid valve. ×4. B. Pulmonary valve. ×4. C. Mitral valve. ×4. D. A mitral chorda tendinea. ×8. E. Aortic cusp. ×23. F. Normal aortic cusp from adult for comparison. ×23.

There were nodules of tumor in the diaphragm.

Histologically (Figs. 5–7) it was found that severe cartilage-like fibrous scarring of the pulmonary valve was responsible for the pronounced deformity seen grossly. In patches large mononuclear cells and smaller numbers of smaller mononuclears were found, especially near the endocardial surface. The cellular reaction was most prominent at the base of the scarred mitral valve. The tricuspid leaflets showed similar scarring and infiltration by mononuclear cells. In such areas as these there could be no doubt of the continuing activity of the process (Fig. 7).

Careful study of the myocardium and of the endocardium of the left atrium revealed no stigmata of rheumatic fever. There were, however, patchy areas of healed and healing infarction of the ventricular myocardium. The only cause for these that was found was the presence of focal hyaline thickening, and in places, occlusion of smaller parenchymal arteries. The large coronary arteries were normal. In both ventricles there were patches of endocardial fibrosis as well as thin layers of fresher-appearing, acellular, somewhat granular material, which may represent agglomerated platelets.

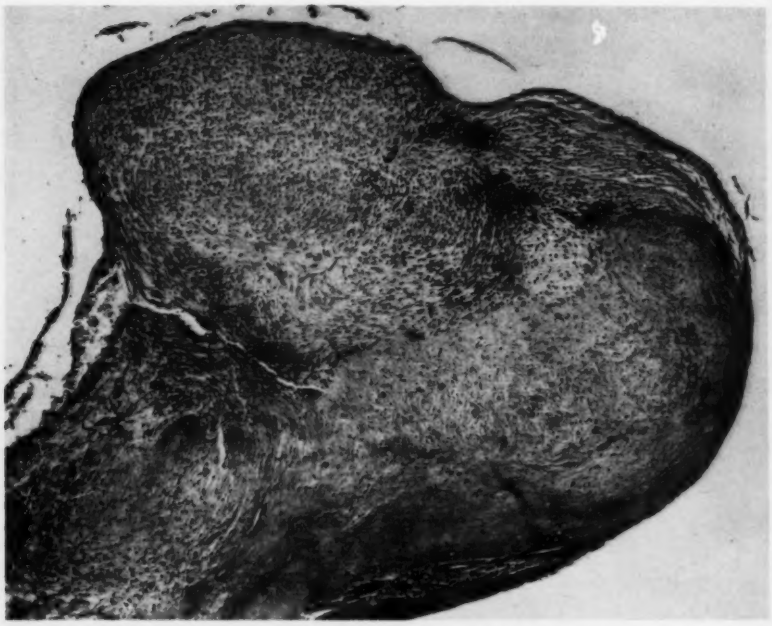


FIG. 6. ×75. The bulbous tip of the tricuspid valve (see Fig. 5A). Ventricular aspect above, atrial aspect below. Hyaline, avascular and acellular material is present on the atrial side of the valve.

Most interesting changes were present in both renal arteries consisting of intimal fibrosis which closely resembled the type of change seen in the heart itself. The possibility that some or all the occluding thrombi in the pulmonary arteries had formed *in situ* cannot be completely excluded. It is of note that the pulmonary artery showed a peculiar scarring of its wall for a short distance above the pulmonary valve.

The tumor was a typical carcinoid (argentaffin carcinoma) arising in the terminal ileum. There was a moderate amount of fibrous tissue associated with the tumor (Figs. 3A and B).

The final anatomical diagnoses were as follows: Chronic organizing valvulitis involving pulmonic, tricuspid, mitral and aortic valves in that order of severity. Argentaffin carcinoma of the terminal ileum with extension to regional lymph nodes, peritoneal implants, metastasis to the liver and massive involvement of the right ovary. Focal endocardial fibrosis. Hyaline thrombi (emboli?) of small myocardial arteries. Multiple, focal, healing myocardial infarcts. Generalized cardiac hypertrophy and dilatation. Multiple pelvic vein thromboses. Multiple massive pulmonary emboli. Patent foramen ovale. Paradoxical (?) emboli to splenic and mesenteric arteries. Infarcts of spleen. Atherosclerosis of abdominal aorta with renal ostial stenosis and scarring of renal cortices.

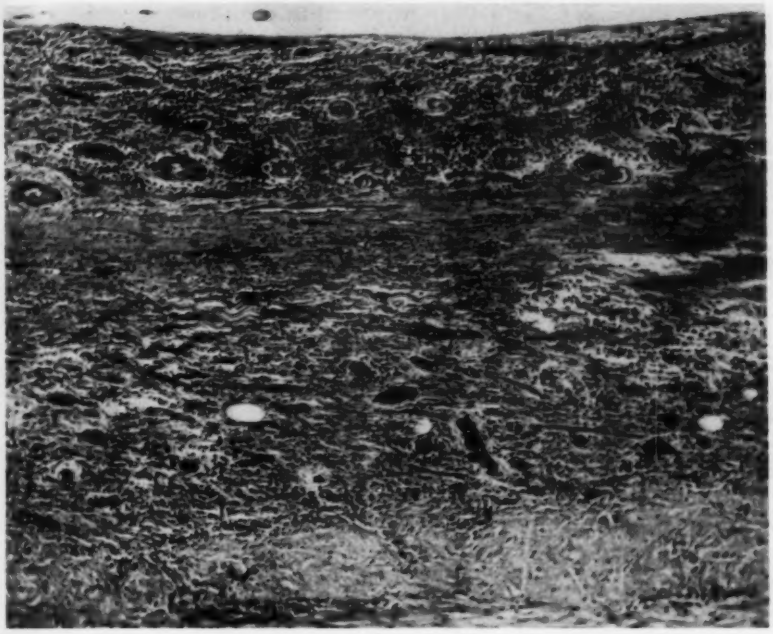


FIG. 7. Striking evidence of current activity of the inflammatory process in Case 2. ×100.

DISCUSSION OF THE CASES

The most dramatic and perplexing clinical feature in these patients and the feature which in retrospect was the clue to the diagnosis was their appearance. Both had telangiectasia of the face. Furthermore, they had pronounced flushing which showed paroxysmal variations in intensity. There are no kodachromes of this patient but the appearance of these patients is, so it seems, so strikingly similar that reference can be made to the water color of what is probably the first recorded case of this syndrome, the patient described by Sir Maurice Cassidy in 1930 (11). (See Fig. 1 for a black-and-white reproduction of this very characteristic facies.) Add to Cassidy's illustration cyanosis and plethora and one has the appearance of the second patient described above.

Very pronounced weakness was a conspicuous feature in Case 2 and of some of the reported ones. Because of the suspected effects of 5-HT on the nervous system, weakness may be a pertinent part of the syndrome. However, because of the heart disease and the malignancy, weakness cannot with complete conviction be attributed to 5-HT specifically.

The diarrhea is undoubtedly an integral and important symptom in this

syndrome. Dizziness (Case 2) may have been the result of pulmonary emboli. On the other hand, this symptom has been recorded rather frequently in the cases reported in the literature (10).

In both the pulmonary and the systemic circuits (Case 2) there were intimal changes and thrombotic occlusions which may have been in part embolic or may have developed in situ. Two sources for emboli were present: pelvic veins and the chambers of the heart.

Pronounced damage to the kidneys, consisting of infarction in various stages, is reported by Hedinger and Langemann (40) and by Page and Glendening (57) in rats to which 5-HT was administered by the subcutaneous route. Renal vasoconstriction is presumably the mechanism. The scarring of the kidneys in this sixty-eight year old patient may have been merely the result of arteriosclerosis. A pathogenesis more specifically related to the carcinoid tumor is plausible in light of the experiments of Hedinger and Langemann.

COMPARISON OF CASE 2 WITH PREVIOUSLY REPORTED AUTOPSY OBSERVATIONS

Publishing in 1954, the Swedish students of this syndrome (83) described six cases and were able to discover ten others in the literature (71) (18) (12) (13) (18) (46) (69). At least one case, that described by Millman (56) under the title "Tricuspid stenosis and pulmonary stenosis complicating carcinoid of the intestine with metastases to the liver", was overlooked. (Other cases, reported mainly in the surgical literature (e.g., ref. 1) may be instances of this syndrome but are not described in sufficient detail from the cardiovascular viewpoint.) Since the survey by the Swedish group, at least six more autopsied cases have been reported (6) (10) (38) (48), together with other probable cases (65) (30).

Brief abstracts of these six and of Millman's case follow:

1. A forty-four year old white female (56) (see ref. 79 for description of the same case) had had weakness and fatiguability seven years, dyspnea five years, ascites and leg edema two years. Abdominal exploration four years before death revealed liver metastases. At that time "there was a peculiar flushing which varied greatly with emotional changes." This, the patient stated, "she had had as long as she could remember." Before death it was recorded that "she had a peculiar, reddish-purple cyanosis—a violaceous color—most marked over the malar areas, with a butterfly configuration, and a mottled formation over the rest of the body. . . Inconstant, rough, systolic and diastolic murmurs were heard at the apex. A roughened systolic and a short blowing diastolic murmur were heard at the aortic area." Autopsy revealed advanced fibrous changes in the pulmonary and tricuspid valves producing stenosis at both orifices. "The marked fibrous endocarditis of the right atrium prevented the dilatation and hypertrophy of that chamber which is commonly associated with tricuspid stenosis." The primary site of the carcinoid was in the ileum and metastases were located in lymph nodes and the liver. None were in the ovary.

2. A seventy-six year old man (38) had had abdominal pain and diarrhea for over two years. He had as many as twenty bowel movements a day. On examination he was found to have a very red face with attacks of violaceous flushing occurring in the face with spread to the limbs and part of the trunk; the skin of the abdomen always remained white. Clinical

examination of the heart was said to reveal no abnormality. B.P. was 170/110. Neck veins were engorged and the EKG showed right axis deviation. The liver was greatly enlarged with palpable nodules. Gastrointestinal x-rays showed an obstructive lesion in the ileum. Hypoalbuminuria was thought to be related to the pronounced diarrhea. Later edema appeared. Autopsy revealed the primary in the ileum. The heart showed marked thickening of the endocardium of the right atrium, pulmonary stenosis and tricuspid fibrosis. Metastases were present in lymph nodes and liver. A striking feature of autopsy was the presence of pronounced scarring in the soft tissues of the pelvis such as to result in a binding together of the bladder, prostate, rectum, iliac and hypogastric vessels and other structures in that area. The patient also had Paget's disease of bone.

3. A forty year old man (10) had had diarrhea for eighteen months with no abdominal pain, exertional dyspnea for six months, swelling of his legs and abdomen for one month. He also had attacks of giddiness and trouble focusing his eyes together with flushing of the skin, especially during periods of diarrhea. He displayed reddish-blue cyanosis of the face and hands, telangiectases of the nose and cheeks, and periodic flushing of the face, spreading to the trunk and extremities. There was intense engorgement of retinal veins during attacks. The blood pressure was 120/80 mm. Hg. A harsh systolic murmur was loudest in the second and third left intercostal spaces. The liver extended three inches below the costal margin. Electrocardiogram showed right axis deviation. There was no polycythemia. Necropsy revealed the primary in the ileum with metastases in mesenteric and para-aortic lymph nodes and in the liver. The endocardium of the right atrium was diffusely thickened.

4. A sixty-three year old housewife (48) had had diarrhea and lassitude for eighteen months, patchy bluish coloration of the skin for thirteen months and edema of the legs for four months. Interestingly, the flushing and mobile cyanosis in this case was most striking over the trunk. The primary carcinoid was in the cecum. Both ovaries and the liver contained metastases. The heart was normal.

5. A fifty-nine year old housewife (48) had had dyspnea and diarrhea for two years, abdominal swelling for four months, and ankle edema for three weeks. Examination revealed "malar flush," engorged pulsating neck veins, precordial systolic murmur, ascites, very large liver. Autopsy revealed the primary to be in the ileum. There was pulmonary stenosis and tricuspid regurgitation. No description of ovarial metastases is given.

6. A 42 year old housewife (6) complained of diarrhea for 18 months and flushing attacks for one year. Weight loss, progressive weakness, and ankle edema developed. Examination revealed in the skin dramatic attacks "resembling in clinical miniature the fickle phantasmagory of the Aurora Borealis." "Petechiae" were noted in the mucous membranes and extremities. There was a harsh basilar systolic murmur and at the apex a low pitched rumbling diastolic murmur. Blood pressure was 100/60 mm. Hg. The liver extended 5 cm. below the costal margin and there was 4 plus leg edema. Late in her course the serum calcium was 14 mgm. per 100 cc. with normal phosphorus and phosphatase. Necropsy revealed carcinoma of the ileum with liver metastases. All four heart valves were sclerosed with predominant involvement of the tricuspid and pulmonic. No mention is made of ovarial metastases.

7. A 43 year old business man (6) had had flushing attacks seven months, these having begun 2 months after appendectomy. He was thought to have congenital or rheumatic heart disease because of the discovery of a heart murmur. Dyspnea and ankle edema later developed. Physical examination revealed a prominent presystolic venous pulsation at the base of the neck. There was a rough basilar systolic murmur. "Two diastolic murmurs were heard over the lower right half of the precordium, giving a quadruple rhythm." The liver was much enlarged. Electrocardiogram showed incomplete right bundle branch block. Operation for presumed constrictive pericarditis was performed. Death occurred about two

years after first symptoms. Autopsy revealed carcinoid of the ileum with metastases to liver and parietal peritoneum and panvalvulitis most marked in the pulmonic and tricuspid valves.

The following probable cases have been reported:

1. In a 68 year old woman (65) the clinical diagnoses were arteriosclerosis, coronary artery disease with atrial fibrillation, congestive heart failure, enterocolitis. The anatomical diagnoses were as follows: "Burnt-out" endocarditis of the tricuspid and mitral valves with slight mitral stenosis; renal arteriosclerosis; cardiac hypertrophy and dilatation; carcinoid of the jejuno-ileum with hepatic metastases; severe catarrhal gastroenteritis.

2. A 65 year old woman (65) had had cardiac complaints from the age of 61 years: dyspnea, pains in the precordial region, leg edema, oliguria, headaches, severe giddiness. Starting at age 64, there were 1 to 3 stools per day, but many times also none. Barium enema showed colitis. She was admitted terminally with symptoms of peritoneal irritation, cyanosis, marked edema, prostration. There were the following findings: Atrial fibrillation, blood pressure of 85/70 mm. Hg, outspoken purpuric extravasation of blood into the skin ("Hautblutung"), platelets 180,000, bleeding and clotting times normal, white blood count 11,000. Necropsy revealed stenosing carcinoid of the jejunum, ulceration and perforation proximal to it, metastases to the liver, obsolete endocarditis of the mitral and tricuspid valves as well as of the atrial endocardium, tricuspid insufficiency, thrombi in the right heart.

3. In a 61 year old man (30) in which previously unexplained attacks of diarrhea had been occurring for over thirty years, cutaneous manifestations, leg edema and ascites were associated with hepatic metastases. However, no precise description of cardiac signs is given and autopsy apparently was not performed.

In a group of ten metastasizing carcinoids Spain (77) makes reference to reasonably advanced valvulitis in seven. In an abstract (63) Rambo *et al.* have referred to other cases of endocardial fibrosis.

The age of death in the reported cases varied from 19 to 76 years; only one patient (38) was older than the 68 year old woman reported here.

In the following three respects the second patient described in this paper differs from the previously reported ones: 1) The foramen ovale was patent with accompanying arterial oxygen unsaturation, polycythemia and possibly paradoxical embolization. 2) The mitral and aortic valves were involved to an extent less than in the case of the pulmonary and tricuspid valves, yet in a degree greater than in any case previously reported in detail. There was also focal intimal fibrosis in peripheral arteries resembling the changes in the heart. 3) Hypertension persisted to almost the very end in spite of multiple pulmonary arterial occlusions and a failing heart.

THE PATHOGENESIS OF THE VALVULITIS

In the reported cases the valves on the left side of the heart have been extraordinarily immune to the effects of the tumor. In Case 2, in which rather marked changes developed in the mitral valve and to a lesser extent in the aortic valve and possibly certain large peripheral arteries, blood had direct access to these areas via the patent foramen ovale. It appears that the tumor's

toxic influence, conveyed in the blood to the right side of the heart, is ordinarily neutralized to some extent, at least, by passage through the lung.

There is evidence that passage of blood through the lungs is accompanied by inactivation of serum vasoconstrictor factor and of 5-HT (and the two are thought to be identical): 1) Pulmonary hypertension, uninfluenced by atropine or vagotomy, occurs with intravenous infusion of 5-HT but systemic hypertension does not consistently develop. 2) Lung extracts inactivate 5-HT *in vitro*. 3) Attempts to perfuse limbs or organs with whole defibrinated blood often runs amuck of considerable vasoconstriction which can be avoided by having a lung in series with the perfused structure. Starling and Verney (78) wrote: "As soon as the defibrinated blood reaches the kidney, the vessels constrict firmly, so that it may be impossible to force a drop through them." The following statement is by Herrick and Markowitz (43): "It is almost impossible to force more than a few cubic centimeters of blood a minute through the kidney in a heart-lung-kidney perfusion except when the blood has previously been circulated through the lungs."

The portion of the heart, ordinarily the right, which is most affected in this syndrome is that part which would appear to be exposed to the highest concentrations of a hypothetical noxious material produced by the tumor. Sclerotic or scirrhous changes (38) in the vicinity of the tumor in some cases may be evidence of a sclerosing action of some material produced by the tumor. In one reported case of this syndrome (12) in a male in whom no abdominal surgery had been performed, the pelvic organs were removed at necropsy only with great difficulty, and it looked as though the pelvis had been filled with plaster of Paris. The observer was surprised to find no tumor in this tissue but only dense formation of fibrous tissue.

Although all the necropsy cases have had liver metastases, it is not certain that these are absolutely essential for development of the cardiovascular manifestations. The presence of liver metastases probably does accelerate the process since any material produced in the tumor can find its way directly to the right side of the heart without prior circulation through, and inactivation by, the liver. However, it is to be expected that the liver would not completely clear the blood on a single circulation and that when large amounts of noxious material are produced in the tumor, relatively large amounts might still pass into the general circulation. Metastases to the ovaries and to other areas drained by the inferior vena cava or primary site of the carcinoid in such areas provide a route for the passage of 5-HT directly to the right heart and pulmonary circulation without prior passage through the liver. The hepatic metastases in the autopsied case reported here were not impressive. The huge ovarial metastasis, on the other hand, was anatomically capable of feeding large quantities of 5-HT into the caval circulation. It is possible that the pathologic process in the heart may develop much faster under these circumstances.

In the pathogenesis of the valvulitis, 5-HT is suspected because of the sizable body of evidence relating it to carcinoid tumors. The effect on the heart of chronic administration of 5-HT to animals will be of great interest. Many herbivores (including rabbits and guinea pigs) do not excrete 5-HIAA (24). Because of apparent species differences in the metabolism of 5-HT it will probably be preferable to use rats and dogs which seem to resemble man in the metabolism of this material. Subcutaneous administration may be indicated since Erspamer (14) found that when 5-HT was so given, the intensity and duration of the antidiuretic effect was greater than after intraperitoneal or intravenous injection; by oral administration 5-HT is practically inactive. Small doses (0.8 mgm./kgm.) have been given to rats for 30 to 60 days (16) but valvulitis could be expected only with much higher doses approaching the LD50. The latter value (for the rat) is 30 mgm./kgm. by the intravenous route and about 117 mgm./kgm. by the subcutaneous route.

Stress on all or particular parts of the heart might be an additional factor in the development of the valvulitis and in determining which valves are predominantly involved. Two types of stress might be present in these patients with carcinoid: 1) The Lillehei (51) type of stress from cutaneous arteriovenous fistulae produced by the disease, especially during flushing. (Reference is made (83) to ballistocardiographic evidence of increased venous return during flush.) Both sides of the heart are probably implicated in this stress. 2) Pulmonary hypertension. The combination of severe long-standing essential hypertension and carcinoid might result in left-sided valvular lesions.

Also important in the pathogenesis of the endocarditis may be the thrombocytosis which was demonstrated by Hedinger and Langemann (39) in rats to which 5-HT was administered by the subcutaneous route. Shortening of the bleeding time also occurred in these animals.

PATHOGENESIS OF THE VASOMOTOR PHENOMENA

Writing in 1943 and again in 1946 (88), F. Parkes Weber described "recurrent violent attacks of flushing of the face, and to some extent of the trunk also, associated with miliary telangiectasia . . . in men, associated with cancer in the abdomen and fibrotic adhesions in the pelvis." He refers to such a patient whom he saw with Dr. Alice Carleton. He also proposed the term "Steiner and Voerner's syndrome". Steiner and Voerner in 1909 (79) described a 27 year old man with miliary telangiectases and severe attacks of flushing of the face, arms and legs. The patient also suffered from diarrhea and, although definitive diagnosis was not made, may well have had the syndrome under discussion. The attacks of flushing were accompanied by anxiety and palpitation and lasted 5–10 minutes. As demonstrated by the illustration provided by the authors, the telangiectases were exceedingly numerous and widespread. They had first begun to appear at the age of 18 years. The urine contained

numerous granular casts. Polyuria and polydipsia with nocturia were described. The patient's father had died of intestinal cancer of some sort.

The mechanism of the cutaneous phenomena is really no better understood than that of the valvulitis. Basically 5-HT causes vasoconstriction, not vasodilatation. Furthermore, flushing does not occur as a result of acute intravenous infusions of the material in man. However, this by no means excludes the possibility that flushing may be produced by chronic elevation of circulating 5-HT. Is it possible that the flushing is diencephalic in origin? If such is the case, it may be that chronic exposure to the material is necessary for development of the syndrome. Two other sets of observations, each suggesting a possible mechanism, may be pertinent to this discussion. Feldberg and Smith (26) demonstrated the ability of 5-HT to instigate the release of histamine in perfused isolated skin flaps. Clinically the flushing attacks suggest histamine release. Page and McCubbin (60) suggested that 5-HT may have a peripheral effect of depressing neurogenic vascular tone with resultant net vasodilatation. Obviously the ovarial metastases have nothing to do with the flushing episodes, i.e., these are not "hot flashes" of the menopausal type. (Actually in the instance of menopausal flushing also, although proximal causes and certain negative factors are understood, the precise positive mechanisms are unknown.)

The flushing paroxysms and even shock are said to be precipitated by mechanical stimulation and pressure in areas where these tumors are located. For instance, enemas and pressure on the liver or on the rare carcinoid in a teratoma of the testis (44) have been described as having these effects. This provides evidence for a direct effect of secreted material in the production of the flushing.

DIAGNOSIS

The Udenfriend test (85) of the urine for 5-hydroxyindole-acetic acid promises to be highly useful in the recognition of these cases. However, much more experience is necessary. For screening purposes a qualitative colorimetric test with 1-nitroso-2-naphthol can be employed. It is to be hoped that the quantitative test will indicate the presence of the tumor before it has metastasized and that in general the test will become as useful as the acid phosphatase in prostatic carcinoma or gonadotropins in chorionepithelioma.

Hedinger and Langemann (39) suggest that thrombocytosis either constant or paroxysmal may also be a useful diagnostic procedure.

X-ray techniques for demonstration of tumors of the small intestine should also be employed (55) (38) in these cases.

The high coloration which accompanies congenital pulmonary stenosis with patent foramen ovale (74) (73) should not be confused with the cutaneous aspect of this syndrome. The presence of polycythemia and the absence of paroxysmal flushing should assist the differentiation. To be sure, polycythemia

can, as is illustrated by Case 2, occur with the carcinoid syndrome as a consequence of secondary patency of the foramen ovale.

Diarrhea is probably a specific manifestation of carcinoid and the result of 5-HT produced by the tumor. This syndrome is uncommon with benign carcinoid but occurs almost regularly with the metastasizing form. Whether it develops appears to be a function of the volume of tumor tissue present.

From what is known about the hemodynamic effects of 5-HT, cardiac catheterization can be expected to reveal evidences of both elevation of pulmonary artery pressure and pressure drop across the pulmonary orifice indicative of obstruction at that site. Calculation of pulmonary resistance should show two components, one at the level of the pulmonary arterioles and one at the level of the pulmonary valve. Such was precisely the finding in one patient who has this syndrome and in whom cardiac catheterization was performed in 1949 by Dr. Richard J. Bing. Interestingly, this patient also showed evidence of patency of the foramen ovale (oxygen step-up in the right atrium and passage of the catheter into the left ventricle). If the thesis of this paper is correct, left-sided valvular lesions can be expected to occur in that case.

THERAPEUTIC MANAGEMENT

In the management of patients with malignant carcinoid the removal of as much tumor tissue as possible (including hepatic metastases) is probably desirable. These tumors are in effect factories for the conversion of tryptophane to 5-HT. The pathological process in the heart valves, the uncomfortable attacks of flushing, the asthma and diarrhea and profound weakness can perhaps be kept at a minimum by surgically reducing the total mass of tumor tissue present. Survival after palliative surgery, in spite of hepatic and other metastases, may be very long (61) (53). Rarely the tumor displays radiosensitivity (86).

Whether a low tryptophane diet with niacin supplements, an ordinary diet, or a high tryptophane diet should be given is moot. Corn and collagen (gelatin) have little or no tryptophane whereas the proteins of egg and milk are rich in this amino acid (8). Low tryptophane intake with niacin supplement, over periods of a few months interrupted by brief periods of normal diet to permit restitution of body proteins, might be the most satisfactory program.

The intimate relationship of tryptophane to niacin, the pellagra-preventive factor, suggests that the diversion of tryptophane into 5-hydroxytryptamine by the tumor might produce a deficiency of the vitamin and account for some of the cutaneous, mental and intestinal manifestations of patients with carcinoid. Tryptophane can be converted to niacin in man (70) without assistance from the intestinal flora (42) (41). Furthermore, the administration of tryptophane to pellagrous patients will effect cure (36) (5). The possible role of niacin deficiency in the pathogenesis of the syndrome associated with carcinoid is yet to be established.

Serotonin antimetabolites (90) (82) (33) now available probably have nothing to offer these cases.

THE BIOLOGY OF CARCINOID TUMORS

The biology of these tumors has several features of interest in addition to this cardiovascular syndrome.

In all series of both metastasizing and non-metastasizing carcinoid, males have predominated over females in a ratio of about 2 to 1. Of the nine cases of metastasizing carcinoid in this hospital, three of the patients were women. Ovarial metastases have been frequent in the women who developed valvulitis (83). In general, however, metastases to the ovary have not been striking in their incidence. The significant association in the female of ovarial metastasis with valvulitis is further evidence for the pathogenetic role of material which is at least partially inactivated on passage through the liver.

Carcinoids may occur anywhere in the gastrointestinal tract from stomach to rectum. At least three instances of primary site in the gallbladder (61) (9) are on record. Argentaffine cells are said to occur normally in the biliary tree (22) and in the pancreas. Carcinoids, arising presumably from intestinal rests, may also occur in teratomas of the ovary (32) and of the testis (75) (76). The ileum is most commonly the primary site of metastasizing carcinoid. However, the appendix, which normally contains the largest number of argentaffine cells, is the most frequent site of carcinoids in general. That appendiceal carcinoids do not more often metastasize may be due in part to the fact that symptoms of appendicitis are likely to draw attention to their presence. Acute intussusception of the tumor in the ileum brought to surgical attention one case (J.H.H. 329639) in which transmural and serosal extension of the carcinoid had already occurred. The patient had been well previous to the development of acute intussusception and has remained well eleven years since operation at which a long segment of bowel was removed.

Stout (81) has reported that tumors which he believes are fundamentally carcinoids may not display the tinctorial characteristics which define them as argentaffinic. It is to be recalled that the chromaffinity of these tumors is a function of the presence of 5-HT or of material chemically closely related to it (4). It would be entirely expected that all carcinoid tumors would not secrete and therefore not be accompanied by the cardiovascular syndrome. The observarions of Stout are consonant with this view. Several cases (e.g., J.H.H. 334451) with extensive hepatic metastases of argentaffinoma have not displayed either the clinical syndrome or the valvulitis found in the cases reported here.

There is an impressive incidence of malignancy of other cellular type in association with metastasizing carcinoid. This was the finding, for example, in four of the nine cases of malignant carcinoid at this hospital. The associated

malignancies in these four cases were adenocarcinoma of the pancreas, squamous cell carcinoma of the esophagus, adenocarcinoma of the stomach and bronchogenic carcinoma. Others (9) have commented on this phenomenon. Pearson and Fitzgerald (61) in reviewing the cases at the Mallory Institute found associated malignancy of different histologic type in nine of twenty-nine cases. In fifteen autopsied cases of metastasizing carcinoid Foreman (29) found a second malignancy in seven. In the series of Warren and Coyle (86) ten of nineteen cases of carcinoid were associated with malignancy of other origin. The basis of this association, which appears to be significant, is obscure. Speculation is stimulated by recent observations (34) on the relationship of tryptophane metabolism to certain neoplasms in the fruit fly (Drosophila melanogaster).

In a series of 8,000 autopsies in adults Spain (77) found 26 cases of intestinal carcinoid, ten of which had metastasized. In the group as a whole, Spain was impressed by the incidence of congenital cardiac anomalies: Chiari net in two, dextrocardia in one, four-cusp pulmonary valve in one. This admitted high incidence may have been the result of chance alone.

SUMMARY

Two patients who displayed cardiovascular complications of metastasizing carcinoid are presented and discussed. In one patient, diarrhea, asthma, flushing attacks and terminally congestive heart failure accompanied hepatic metastases of a carcinoid tumor, whose origin was never identified.

A second patient is described in whom acquired valvulitis, telangiectasia and episodic flushing occurred in association with malignant carcinoid of the ileum with ovarial and hepatic metastases. All the heart valves were involved in the following order of descending severity: pulmonary, tricuspid, mitral and aortic. It is suggested that patency of the foramen ovale (secondary to the pulmonary and valvular disease) may have been responsible for the following features which represent deviations from the previously reported cases: Polycythemia, systemic hypertension, and (most important) involvement of the valves on the left side of the heart and possibly certain peripheral arteries.

It is proposed that the valvulitis in this syndrome represents the direct effect of material (possibly 5-hydroxytryptamine) which is elaborated by the tumor, which is circulating in the blood and which is partially inactivated in the lungs and in the liver. Cutaneous A-V fistulae and pulmonary or systemic hypertension may represent valvular stresses which participate in the pathogenesis of the valvulitis. Thrombocytosis of the type observed in animals requires evaluation as another possible factor in the valvulitis.

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THROMBOSIS OF THE BASILAR ARTERY WITH SOFTENINGS IN THE CEREBELLUM AND BRAIN STEM DUE TO MANIPULATION OF THE NECK

A Report of Two Cases with One Post-Mortem Examination. Reasons are Given to Prove that Damage to the Vertebral Arteries is Responsible

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INTRODUCTION

In 1947 Pratt-Thomas and Berger published an article dealing with three cases in which death followed chiropractic manipulations. Two of these cases are of great interest and are identical in all essential features with the cases which are the subject of this report. The first patient was a man of 32 years who sought chiropractic treatment because of headaches, giddiness and nausea. He became unconscious during manipulation of the neck. Some hours later in the hospital, he showed almost complete paralysis of the extremities with spasticity of the legs, ankle clonus and great toe signs. There was retention of urine. The neck was freely movable and there was no pain or tenderness in the neck. Roentgenograms of the cervical spine revealed no evidence of fracture or dislocation. Soon respirations began to fail. The temperature rose to 107 degrees F. and the patient died some 24 hours after the manipulation. Post-mortem examination revealed thrombosis of the basilar artery, of the left anterior inferior cerebellar artery and the right posterior inferior artery. There was a large softening in the left cerebellar hemisphere. Softenings were also found in the right cerebellar hemisphere, the left cerebral peduncle and the left side of the pons. Palpation of the cervical canal revealed no bony abnormalities. The range of movement at the atlanto-axial joint seemed to be increased. There were no fracture of the skull and no bruises of the scalp. The arteries were histologically normal.

The second patient was a woman of 35 years who had consulted a chiropractor because of hay fever. She was brought to her home one afternoon by the chiropractor. She was unconscious and died a few hours later in the hospital without regaining consciousness. No information about the clinical features of this case is available. Post-mortem examination revealed thrombosis of the basilar artery, the right vertebral artery and the left posterior inferior cerebellar artery with softenings in the cerebellum. The cervical cord was removed but showed no injury. The arteries were found to be normal on histological examination. There was no fracture or dislocation of

the cervical spine but the range of movement at the level of the atlas and axis was thought to be increased. There was no fracture of the skull and no bruises on the scalp.

Not long after this paper was published, one of us observed a patient who suffered lasting damage to the brain stem following chiropractic manipulation of the neck but survived. Recently another was seen who died. His case is unusual in that the manipulation was performed by his wife and not by a chiropractor. Dr. James Arnold has told us of another case observed in a Baltimore hospital in which fatal thrombosis of the basilar artery followed chiropractic treatment.

The purpose of this paper is to describe and analyse these two cases and to emphasize the danger of excessive rotation of the head.

Case History 1 (No. 694383—Path. 25535) *Man of 37 years developed signs of damage to the brain stem immediately after his wife twisted his head. The course was progressive and he died about 60 hours later. Softenings were found in the cerebellum and brain stem and there was a thrombus in the basilar artery.*

D. K., a man of 37 years, a previously healthy bacteriologist, arrived home about 6 P.M. on January 14, 1955. He noticed that his wife had placed her hands on either side of her head and was twisting it vigorously from side to side. "Why do you do that?", he asked. "My neck is stiff and this makes it feel better", she said. "My neck is stiff. Twist it for me", he said. She twisted it strongly to one side. "That feels better. Do it again", he said. She did so. The patient staggered at once and fell against the wall. His wife helped him to a couch. He seemed to be dazed. Within a few minutes he complained of vertigo, loss of vision on his right, and of noises in his right ear. He then started to vomit and the vomiting persisted throughout that evening and night. He was unable to stand alone or even to sit up for he fell to the left. His left arm was clumsy. He could not void.

He was brought to Johns Hopkins Hospital about 4:30 P.M. on January 16. The pulse was 100, temperature 100 degrees F. and blood pressure 140/100. He was drowsy but well oriented and cooperative. He did not speak spontaneously but answered promptly when addressed. The pupils were small and the left was smaller than the right. Both reacted to light. No reduction of vision or defect in the fields was demonstrable. The optic discs were normal. The left lid drooped. On deviation of the eyes to either side there was horizontal nystagmus with the slow phase to the midline. There was no diplopia or limitation of ocular movement. A slight left facial weakness was noted. No deafness could be found. Articulation was indistinct though the tongue moved well. Swallowing was difficult.

The patient was unsteady and had a tendency to fall to the left even when he was sitting up in bed. There was no weakness of the extremities but pronounced ataxia of cerebellar type was found in the left arm and leg. The tendon reflexes were in order and the plantar responses were normal. Sense of passive movement and vibratory sense were intact but there was partial cutaneous analgesia on the right side extending up to the base of the neck. His neck was flexible and he had no pain in the neck.

The patient continued to vomit. He could not void and had to be catheterized. There was increasing difficulty in swallowing and suction was required to remove pharyngeal secretions. The left vocal cord was found to be immobile on laryngoscopy.

About 5 A.M. on January 17, the patient was heard to fall to the floor. When a nurse tried to help him into bed, it was found that he could not stand even with support. It was

then found that he had a left hemiplegia. The patient's respirations increased to 160 per minute and then stopped. The heart beat ceased a few minutes later. Death occurred about 60 hours after the injury.

Roentgenograms of the cervical spine revealed no evidence of dislocation or fracture. Roentgenograms of the chest and skull were negative. The blood STS was negative. The spinal fluid contained 2 polymorphonuclear cells but was otherwise normal. The blood counts were normal. The non-protein nitrogen was 37 mgs. and the blood sugar 112 mgs.

External inspection of the brain revealed swelling of the left cerebellar hemisphere. The basilar artery appeared to contain two thrombi, one in the superior end near the bifurcation and another in the lower portion. There also appeared to be thrombi in the left posterior cerebral artery and in the left posterior inferior cerebellar artery. Unfortunately the arteries were lost before histological examination could be made. No abnormalities in the walls of the vessels could be seen in the gross. On section of the brain the only abnormality found on inspection was a small hemorrhage about 1.0 cm. in diameter in the white matter of the left cerebellar hemisphere. Microscopic examination revealed loss of cells and small areas of partial softening in the white matter of the left cerebellar hemisphere. These lesions were found in the distribution of the posterior inferior artery. Only a few small areas of partial softening were found in the white matter of the right half of the cerebellum. All of these lesions were typical of ischemic softenings. Little damage was found in the brain stem. There were small foci of cell loss in the inferior olive on the left and a rarified area in the white matter of the brachium pontis on the left. The left facial nucleus showed a few cells which stained poorly. In the brain only a small softening was found in the calcarine cortex of the left occipital lobe.

Thus, it is evident that the anatomical changes were less destructive than one might have expected. No doubt, the softenings would have been more extensive had the patient survived longer. An imperfect correlation between the lesions and the clinical findings is possible, however. The nystagmus and cerebellar ataxia on the left are explained by the softening in the left cerebellar hemisphere. The cervical sympathetic nerve lesion, the left facial palsy and the analgesia on the right side of the body must be ascribed to the damage to the left side of the pons. The transient right hemianopia is explained by the softening in the occipital lobe on the left. The paralysis of the left vocal cord and the left hemiplegia and terminal failure of respiration are not correlated with any demonstrable anatomical lesions.

Case History 2 (No. 46219) *A man of 41 years was manipulated by a chiropractor. He lost consciousness at once and later was found to have signs of damage to the right side of the pons. About ten years later the signs and symptoms still persisted.*

C. R., a man of 51 years, was seen in consultation with Dr. J. E. Howard on June 3, 1948. He stated that about ten years before he had consulted a chiropractor because of frequent colds in the head. The chiropractor placed him on the table and massaged his scalp for a while to get him to relax. He then suddenly twisted his head to one side. The patient became unconscious almost at once and was taken to a hospital where he vomited repeatedly. His wife states that the patient was unconscious for 24 hours. There was paralysis of the left arm and leg and ataxia of the right arm and leg. He could not swallow and had to be given intravenous feedings. Speech was indistinct so it was difficult to understand what he said. There was retention of urine requiring catheterization. The right ear was deaf and the right side of the face did not sweat. Later, it was discovered that there was loss of sensibility on the left side of the body. Within two or three weeks he could walk with help and in two months he could walk alone.

When the patient was 48 years old, i.e. about three years before we saw him, he was found

to have hypertension. After that his memory seemed to fail and his judgment became uncertain. Three months before he came to Johns Hopkins Hospital, he suddenly lost the central vision of the right eye.

On examination the patient was very cheerful and possibly somewhat euphoric. One gained the impression that his memory was not clear. The blood pressure ranged between 170 and 190 systolic over 100 to 110. The positive neurological findings included: 1—Hemorrhage in the right retina with reduction of vision. 2—Loss of function of the cervical sympathetic nerve tract on the right with small pupil, drooping lid and lack of sweating over the face. 3—Cerebellar ataxia of the right arm and leg of moderate degree. 4—Analgesia and thermanesthesia over the left side of the face, body and left extremities but no loss of tactile sensibility. 5—Slight dysarthria. 6—Partial nerve deafness on the right side.

The blood STS was negative. The electrocardiogram showed no sign of cardiac damage. Roentgenograms of the chest showed slight enlargement of the heart and a dilated and tortuous aorta. Renal function was normal.

DISCUSSION

We seem to be dealing with a well defined syndrome for in all four of these cases the essential features are the same. Thrombosis of the basilar artery and some of its branches was found in the three cases in which post-mortem examination was made. In the fifth case mentioned by Dr. Arnold, basilar artery thrombosis was also found. Our patient who survived showed signs almost identical with those of our other patient who died.

No dislocation or fracture of the cervical spine was found in roentgenograms or at post-mortem examination. The skull was not fractured in any case and the scalp showed no bruises. There was no evidence that any of these patients had received a blow on the head. We must conclude, therefore, that the injuries were not due to simple direct trauma but to interruption of the circulation.

Vascular disease does not seem to play any role in these cases. Our second patient had hypertension and extensive arteriosclerosis when he was examined ten years after the injury. We have no evidence that he had vascular disease at the time of the manipulation. In the three cases in which post-mortem examination was performed, the arteries were always normal. The ages of the patients were 32, 35, 37 and 41 years.

In all cases the symptoms followed manipulation of the neck. In our two cases, it is stated clearly that the head was rotated on the vertical axis. In the cases of Pratt-Thomas and Berger, the precise movement which was performed is not stated. In three cases the chiropractor manipulated the neck and it is possible considerable force was employed. In our first case, the wife, who was a small woman weighing not much over one hundred pounds, rotated the head of her husband who was a large man. In this case it is hard to believe that great force was applied.

The symptoms developed immediately and it does not seem possible that a thrombus could develop so suddenly. The initial symptoms must have

been due to occlusion of an artery by some mechanism. No doubt, the thrombus formed later and may well have played an important role in the final result. The only plausible explanation we can offer for the immediate interruption of the blood flow in the basilar system by rotation of the neck is the assumption that the vertebral arteries were injured in some manner.

The anatomical relations of the vertebral arteries are of interest in this connection. According to Piersol these arteries ascend through the foramina in the transverse processes of the first six cervical vertebrae. As they traverse the foramina in the axis they abandon their previous course which was almost vertical and pass upward and outward to reach the foramina in the atlas. As they emerge from the atlas they pass horizontally to the posterior aspect of the atlas and enter the suboccipital triangle. They then penetrate the occipito-atlantoid ligament and the dura to enter the spinal canal reaching the cranium through the foramen magnum. Thus, it is evident that the vertebral arteries pass through a series of superimposed bony rings. Excessive rotation at any joint may result in angulation, stretching or compression of these arteries. It is possibe that spasm of the arteries might result. Rotation of the head occurs chiefly at the joint between the axis and the atlas where it has been estimated a movement of 25 degrees is possible. No doubt, the damage is done at this level. Pratt-Thomas and Berger believed that they could demonstrate an excessive range of movement at the atlanto-axial joint in their cases. This observation may be interpreted as evidence of laxity of the ligaments or of rupture of the ligaments for the odontoid ligaments which limit rotation at this joint are not bulky.

Pratt-Thomas and Berger mention that hyperextension of the head, which involves movement of the atlas on the occiput, results in some narrowing of the cranio-spinal aperture. They suggest that this movement may cause compression of the vertebral arteries and of the spinal cord. We are not convinced that this explanation is adequate for no evidence of compression of the cord or vertebral arteries at this level has been found at post-mortem examination and in our cases, it is clear that rotation and not hyperextension was responsible.

It is unfortunate that in none of these cases have the vertebral arteries been examined in the neck where one would imagine the primary lesion is to be found. It would also be of interest to determine whether the odontoid ligaments have been ruptured or not.

Cases of dislocation of the atlas on the axis resulting from chiropractic manipulations have been reported by Blaine and we have seen one case of this type (No. 456703) in which the spinal cord was seriously injured. In such cases the symptoms are purely spinal.

One of the writers has reported a case which seems to have some significance in regard to the problems under discussion. The patient was a boy of

17 years who had syncopal attacks when he moved his head too quickly. When he regained consciousness he might have nystagmus, cerebellar ataxia, blurring of vision and double vision. There was always complete recovery within a short time. Eventually it was discovered that the odontoid process was missing. It was suspected that excessive mobility of the axis was causing intermittent compression of the vertebral arteries. At operation this vertebra was, in fact, found to be excessively mobile. Fusion resulted in complete relief of symptoms which has persisted during the three years which have elapsed since operations.

CONCLUSION

Two cases are reported in which sudden rotation of the head, a standard maneuver in chiropractic treatment, was followed by damage to the brain stem and cerebellum. In one case post-mortem examination revealed thrombosis of the basilar artery. The clinical features in the other case were consistent with obstruction of the basilar artery. One patient died and one survived with persisting disability.

Two cases previously reported by Pratt-Thomas and Berger are reviewed. In these cases post-mortem examination was performed and thrombosis of the basilar artery was found in each instance.

It is suggested that excessive rotation of the neck results in damage to the vertebral arteries with interruption of the blood flow into the basilar system and thrombosis due to stasis. There is some reason to believe that such excessive rotation is easily carried out only in persons whose odontoid ligaments are too lax or easily ruptured.

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SEXUAL INCONGRUITIES AND PSYCHOPATHOLOGY: THE EVIDENCE OF HUMAN HERMAPHRODITISM*

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INTRODUCTION

Few people acquainted with Freudianism and its impact on the theories of psychology and psychiatry can fail to be aware that sexuality, in its broadest sense, has been given an important place in theories about the genesis of psychiatric disorders. It is appropriate, therefore, to examine the evidence of human hermaphroditism in relation to psychopathology.

During the past four years, the authors have studied and followed 94 hermaphroditic patients, juvenile and adult, in an attempt to ascertain, among other things, the status of their psychologic healthiness or nonhealthiness.

Before making an appraisal of psychologic healthiness in these 94 patients, it was necessary to separate them into subgroups the members of which were sufficiently similar, anatomically and physiologically, to permit valid psychologic comparison one with another. There are eight subgroups, representing eight varieties of hermaphroditism (Table I). A brief synopsis of the identifying signs of each variety has been published in an earlier paper (1).

The sexual incongruities that one may find in hermaphroditism involve divers contradictions, singly or in combination, between seven variables of sex (Table II).

In affirmation of evidence assembled in an earlier paper (11), it may be said that, in 95 per cent of our 94 cases, gender role and orientation corresponded unequivocally with the sex of assignment and rearing, irrespective of incongruities between this pair of variables, on the one hand, and one or more of the other five variables of sex, on the other hand. In only 5 of our 94 patients, therefore, was there any question of psychologic nonhealthiness on grounds of a demonstrably ambiguous gender role and orientation.

STANDARDS OF APPRAISAL

To appraise psychologic healthiness and evaluate the severity of nonhealthiness is an extremely vexacious problem, to admit which requires no apology.

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TABLE I

*Varieties of Somatic Ambisexual Development**

1. Congenital hyperadrenocorticism in otherwise normal female	48
2. Female, with well differentiated phallus, normal ovaries and normal internal reproductive structures	3
3. True hermaphroditism, i.e., with testicular and ovarian tissue both present	1
4. Male, with unarrested mullerian differentiation:	
(a) with normal penis and one or both testes cryptorchid	0
(b) hypospadiac and cryptorchid	3
5. Gonadal agenesis (dysgenesis), with simulant female infantile body morphology and male chromosomes	16
6. Simulant female, with testes, blind vagina, mullerian vestiges and breasts	7
7. Cryptorchid male hypospadiac, with breasts at puberty:	
(a) with urogenital sinus	1
(b) with blind vaginal pouch	0
8. Cryptorchid male hypospadiac:	
(a) with urogenital sinus	13
(b) with blind vaginal pouch	2
	—
	94

* For the purpose of this classification, the primary differentiation is by the criterion of gonadal sex. This practice reflects the traditional medical and surgical approach which prevailed until recently, whereby gonadal sex is the *real sex* and the classification of hermaphrodites threefold, namely, true hermaphrodites and male and female pseudohermaphrodites. Our findings do not justify the choice of this gonadal criterion as the *exclusive*, or even as the *primary* criterion, from the standpoint of psychologic and behavioral study, nor for purposes of wise clinical practice. Nonetheless, the gonadal criterion offers a convenient basis for medical classification and discussion. See bibliographic references 2 to 7, inclusive, for further, comprehensive information concerning the varieties of hermaphroditism.

There are no instruments to use, and no standardized routines of calibration to follow. We have collected extensive data on our patients using formal psychologic tests, casual interviews, recorded and transcribed systematic interviews, participant observation of behavior, and interviews with relatives.* We have done follow-up studies on the great majority of patients once or twice a year, or more often, dependent on the feasibility of a return journey to the hospital. On the basis of all available data, we have exercised our clinical judgment, separately and as a group, and rated each patient on a graduated scale that has four salient points:

—healthy
—mildly nonhealthy
—moderately nonhealthy
—severely (morbidly) nonhealthy

We have always been in agreement about the rating of each patient. A rating of healthy, mentally or physically, is not synonymous with being

* Further details of the method of gathering information are given in Money and Hampson (12).

TABLE II

Seven Variables of Sex

1. Chromosomal sex (8, 9).
2. Gonadal sex.
3. Hormonal sex.
4. Internal accessory reproductive structures (10).
5. External genital morphology.
6. Sex of assignment and rearing.
7. Gender role and orientation established while growing up.

perfect or ideal according to some preordained standard, not even the standard of the statistically typical or normal. It may, for example, be statistically typical or normal, but not healthy, for members of a population to have beriberi or endemic goiter. Nonetheless, healthiness and statistical typicalness become more nearly synonymous when a random sample of individuals is drawn from a large and heterogeneous population, for such a sample discloses the wide range of variability encompassed by the typical or normal.

In general medicine, a rating of healthy is consistent with a wide range of individual differences in height, weight, pulse rate, blood pressure, blood count, 17-ketosteroid excretion, threshold of resistance to microorganisms, and so forth. In psychologic medicine, also, a rating of *healthy* is consistent with a wide range of individual variation. To be rated healthy, it was not necessary for patients to be devoid of problems, conflicts, perplexities and anxieties, nor devoid of specialized modes of personality functioning. It was necessary only that they were encountering their various experiences and carrying out their various transactions in life without evidence of persistent mismanagement or incompetence of a degree that required other people consistently to make exceptional provisions for them or show special consideration toward them.

A rating of *nonhealthy* signifies that a person fails, in some way or other, to negotiate the encounters and transactions of life, unless other people grant special considerations or exceptional provisions of one sort or another. The kind of consideration or provision required varies according to the type of nonhealthiness and its degree, whether mild, moderate or severe. Thus, congenital IQ impairment of severe degree may require permanent custodial supervision, whereas an equally severe disorder, such as compulsive immobility except when walking backwards, may require psychiatric hospitalization and psychotherapy. A rating of nonhealthy does not, per se, give any indication of the duration, onset, cause or prognosis of a disorder. Cognitional impairment, for example, is psychologic nonhealthiness whether associated with tertiary syphilis, with congenital cerebral defect, with prolonged schizophrenic deterioration, with transient toxic delirium, or with chronic self-depreciation, anxiety and dread.

A patient with a rating of *mild nonhealthiness* is a person who, from a lay-

man's point of view, would usually be credited as normal and well adjusted. On the basis of increased information obtained in psychologic investigation, however, it is found that the person negotiates life in a series of encounters and transactions that intermittently reach a crisis of stressfulness. During these periodic crises, some special considerations and exceptional provisions are needed in order that the person can again pick up the threads of living. The special considerations and provisions may come from family, friends, employer or a professional expert. A brief series of psychiatric consultations is, in certain instances, as expeditious a provision as any that can be made.

The people to whom a rating of *moderate nonhealthiness* is applied are usually recognized by laymen as slow, retarded, nervous, neurotic, maladjusted, emotionally disturbed, or beset by psychologic problems. Diagnostically, the psychiatric nomenclature applicable to such people is not restricted to the neuroses, but may include character disorders, personality trait disorders, delinquency or mental deficiency, among others. Moderately nonhealthy people are competent at negotiating some of the ordinary encounters and transactions of life, but their lack of healthiness is great enough to require that they be granted special considerations and provisions, of some sort or other, by many different people and in many different contexts of living, for an indefinite period of time. One special provision may be psychiatric treatment, more or less regularly, over a period of years, but without prolonged hospitalization or constant psychiatric supervision.

A rating of morbid or *severe nonhealthiness* is applied to people who are chronically, or for a long period, unable to negotiate any of the ordinary transactions and encounters of life without such special considerations and provisions as constant protection, constant supervision, indefinite custody or prolonged therapeutic treatment. Inexpert and lay opinion usually concedes that such people are not psychologically healthy, though the degree of nonhealthiness is commonly underestimated. Technically, the rating of severely nonhealthy applies to most psychoses. It may also apply to the most severe and disabling neuroses, to addictions, to chronically criminal and so-called psychopathic personality disorders, to extensive cerebral and cognitional impairments, gross mental deficiency, and so forth.

DISTRIBUTION OF RATINGS

The distribution of psychologic healthiness and nonhealthiness ratings among the 94 patients, according to variety of hermaphroditism, is shown in Table III.

(*a*) *Severely Nonhealthy*

The most noteworthy finding of this study of psychologic healthiness in hermaphrodites is the conspicuous absence of severe psychologic disorder. The rating of severely nonhealthy was appropriate for only one among our ninety-

TABLE III

Psychologic Healthiness Ratings of 94 Patients

Variety of Hermaphroditism	Healthy	Nonhealthy			Total
		Mild	Moderate	Severe	
1. Adrenal ♀	28	12	7	1	48
2. Nonadrenal ♀	3	—	—	—	3
3. True	1	—	—	—	1
4. ♂, mullerian differentiation	1	—	2	—	3
5. Gonadal agenesis	14	1	1	—	16
6. ♂, simulant ♀	7	—	—	—	7
7. ♂, hypospadiac, breasts	1	—	—	—	1
8. ♂, hypospadiac	8	3	4	—	15
Total	63	16	14	1	94

four patients. This patient, an hyperadrenocortical female pseudohermaphrodite mentally defective since birth, tested with an estimated IQ no higher than 40 by the time she was five years old. No other patients required a rating of severe psychologic nonhealthiness. None was psychotic and none required psychiatric hospitalization, though one patient told that her older sister, an hyperadrenocortical female like herself, had been hospitalized ten years earlier with a diagnosis of dementia praecox, since which time she had been living at home on the farm, though only partially recovered.*

(*b*) *Moderately Nonhealthy*

The fourteen patients rated moderately nonhealthy were, apart from their rating, a diverse and heterogeneous group. They ranged in age from three to thirty-seven years. Three were adults, six were in the teenage, and five below the teenage.

With one exception, all of the patients knew from visible anatomical evidence that they were genitally deformed. The exception was a patient with gonadal agenesis and male chromosomes who looked like a girl and had been reared as a girl for all of her fourteen years. Four older female patients with hyperadrenocorticism, living as women, were severely virilized before treatment was begun. Two younger female hyperadrenocortical patients had been reared first as girls, then as boys, and a third had had several hypospadiac repairs, as a boy, from an early age. Two siblings, cryptorchid hypospadiac

* The rareness of psychosis among hermaphrodites was corroborated in a survey of the literature (13). Among 248 postadolescent cases of hermaphroditism, there were 5 instances of psychosis: 2 senile dementia, 1 manic-depressive, 2 schizophrenia. There were also 3 cases of epilepsy, 3 of gross mental deficiency and 2 of suicide. Visible hermaphroditic anatomy was present and of apparent causal significance only in the two instances of suicide and one instance of schizophrenia, paranoid type.

males with clitoral sized phallus, were living as boys, one having been changed from living as a girl at the age of five. There were two other cryptorchid hypospadiac males. One, with medium sized phallus who had been reared as a girl, changed on his own initiative to live as a man at the age of sixteen. The other, living as a boy, was a high grade mental defective. Finally, two cryptorchid hypospadiac males with well differentiated mullerian organs, both reared and living as girls, were also high grade mental defectives.

Though they all received the same rating of moderately nonhealthy, these fourteen patients displayed widely diverse signs and symptoms of psychologic nonhealthiness. In three cases, the chief disability was an IQ (Wechsler) in the 60s, near the upper limit of the mental defective rating. The commonest disability, irrespective of IQ, was an excessive operation, in some form or other, of inhibitory and control functions of the personality. In half of the patients, this inhibitory excess showed up as a psychologic growth failure: relative to age and IQ, these patients evidenced in some degree a babyish lack of accomplishment and mastery.

Inhibitory excess also showed up, in all except two of the patients, as a chronic and sometimes excruciatingly pervasive syndrome of shyness, bashfulness, diffidence, reticence and inarticulateness. This syndrome was most in evidence whenever social transactions and conversation pertained in any way to eroticism, sexuality or romance.

The immobility of excessive inhibition, especially when tears or preliminary signs of weeping are added, may signify apprehension, anxiety, fear and dread. One patient, an older hyperadrenocortical woman, had a chronically recurrent syndrome of anxiety and dread, complete with concomitant physiologic signs of anxiety. Five of the younger patients manifested acute episodic bouts of anxiety intense enough to be called terror, especially in connection with hospitalization.

The immobility of excessive inhibition may signify not only anxiety and fear, but also sullen, stubborn antagonism. There were three patients in whom it was often difficult to distinguish antagonism from anxiety.

Two of the fourteen patients did not manifest a preponderance of the inhibitory function of personality. Each took the bull by the horns, so to speak, and met the challenge of the sexual dilemma head on. One changed from living as a girl to living as a man, and the other, despite severe adrenocortical virilization, entered compulsively into sexual relations with a series of boyfriends. Both these people negotiated their lives, however, only by resorting to stimulants and sedatives, including alcohol, in large doses. Each had assorted neurasthenic and psychosomatic complaints, and each was subject to intermittent depressive, moody spells.

Whether inhibitory control or assertive mastery predominated in personality functioning, in none of the patients was there an undue degree of bizarre per-

ception and judgment, nor of cognitional idiosyncracy such as hallucination, confabulation or delusion.

(c) *Mildly nonhealthy*

The composition of the group of sixteen mildly nonhealthy patients does not differ in any clearly distinguishable way from that of the group of fourteen rated moderately nonhealthy. The sixteen ranged in age from four to fifty years. Eleven were adults, two were in the teenage and three below the teenage.

As in the less psychologically healthy group, there was only one patient (with a diagnosis of gonadal agenesis and male chromosomal pattern) who had no visible anatomical evidence of genital deformity. In the moderately nonhealthy group, four patients underwent a reassignment of the sex of rearing, three of them after the age of four years; in the mildly nonhealthy group, three patients underwent a reassignment of the sex of rearing, all before the age of four years. Four of the group of sixteen were juveniles with hyperadrenocorticism (of whom two were also sex reassignment cases). Eight more with the same syndrome had reached adulthood as severely virilized women before cortisone therapy was available; one of these, married, had the chronically invalid personality expected in a person dying, as she was, with cancer. The remaining two patients in the group were cryptorchid hypospadiac males with female looking external genitals who had been reared, though with indecision, as girls.

By contrast with the moderately nonhealthy patients, none of the mildly nonhealthy had an IQ at the mentally defective level. The majority manifested in one form or another a mild excess, either chronically or intermittently, of inhibition and control in personality function. In one patient, inhibitive collapse was a direct sequel of widespread metastatic cancer. In four patients, inhibition showed up chiefly as introverted shyness and cautious guardedness along with, maybe, an occasional outburst of righteous self-justification. In two other patients, inhibition showed up chiefly as intermittent moody spells of of despondency bordering on depression. In yet two other instances, inhibition had a more specifically amnesic guise, and the patients had transient hysteric conversion symptoms. Another patient had a speech inhibition, namely stuttering and stammering. There were three patients, living as women, who had homosexual desires and inclinations. One of these, an introverted and shy person, had not been a partner in homosexual practices; the other two, whose erotic practices had been bisexual, were not introverted and shy in day-to-day routines and affairs.

In addition to the two bisexual patients, there were three other patients in whom the signs of mild nonhealthiness signified not inhibition but a makeshift, inexpedient effort of mastery. The three patients were living as girls. One had a compulsion to check locks and switches more than once before going to sleep at night. One did some compulsive stealing, notably of a watch from the home

of friends. The third, an infant, had intermittent episodes of temper tantrum and screaming.

In the mildly, as in the moderately nonhealthy patients, disturbances of perception, imagery, thought or judgment were lacking. Only one patient was inclined to be autistic in thought as well as introverted and inhibited in demeanor.

(*d*) *Healthy*

The composition of the group of sixty-three patients with a rating of psychologically healthy differs from that of the nonhealthy groups on two major counts. The first count is this: the proportion of juveniles is greater among the healthy than the nonhealthy. A rating of healthy was given to nine adults, seventeen teenagers and thirty-seven preteenage children, of whom eighteen were below the age of five. Table IV shows the comparative distribution of patients according to age and to rating as either healthy or nonhealthy.

The preponderance of healthy juveniles (Table IV) is statistically significant at between the 2 per cent and 1 per cent level of confidence (chi-square: 6.19). This preponderance of juveniles may signify either that the investigators were more lenient in appraising children, or that nonhealthiness was more difficult to identify in children than adults, or that nonhealthiness was less prevalent among children than older people. The last of the three alternatives is considered almost certainly the correct one.

Greater prevalence of psychologic healthiness among the juvenile rather than the older hermaphrodites can be accounted for with the hypothesis that the juveniles had not experienced the impact of their hermaphroditic paradox in its full force, either because they had not lived long enough to do so, or because they had received corrective therapy from an early age, or because they had a form of hermaphroditism which did not declare itself as a visible ambisexuality.

There was no evidence that the psychologic growth and development of hermaphroditic babies during the first weeks and months of life was influenced by their hermaphroditic status, unless indirectly as a concomitant of parental doubts and dreads. The infants became most psychologically vulnerable when they grew old enough and experienced enough to know and recognize that they were genitally neither entirely boy nor entirely girl. Their vulnerability increased as they grew older, if their externally visible secondary sexual development was incongruous with the sex of assignment and rearing.

TABLE IV

Distribution of 94 Cases According to Age and Psychologic Healthiness or Nonhealthiness

	Preteenage	Teenage and adult
Healthy	37	26
Nonhealthy	9	22

TABLE V

Age and Psychologic Healthiness of 48 Hyperadrenocortical Patients

	Preteenage	Teenage	Adult
Healthy	20	6	2
Mildly nonhealthy	2	2	8
Mod. nonhealthy	2	3	2
Severely nonhealthy	1	—	—

The relationship of psychologic vulnerability to age was particularly well exemplified in the hyperadrenocortical patients (Table V). Among the 20 preteenage patients rated as healthy, 13 were under the age of five years. They were being reared as girls. Each of the thirteen was unacquainted with her sexual ambiguity, owing either to her infancy or the early institution of corrective therapy, or both.

Hyperadrenocortical hermaphrodites for whom corrective therapy is instituted in infancy resemble another group of juvenile hermaphrodites who have no visible signs of their sexual anomaly. These others are simulant females who have a perfectly normal female body morphology, externally, which is contradicted by a male chromosomal pattern, by improperly differentiated mullerian organs, and by testes that paradoxically secrete estrogens after puberty. Very similar are the patients with male chromosomal pattern, immature normal mullerian organs, and gonadal agenesis. Patients in both categories are unhesitatingly declared girls at birth and grow up as psychologically healthy girls.

The preponderance of these female looking patients (with or without gonads) with a healthy rating is the second major count on which the group of 63 patients rated healthy differs from the nonhealthy groups. Only 2 of the female looking patients were rated nonhealthy whereas 21 (9 juvenile and 12 teenage or adult) were rated healthy. The prevalence of psychologic healthiness among these female looking hermaphrodites may be accounted for with the hypothesis that they were not confronted with sensory evidence of hermaphroditic incongruities to disturb healthy psychologic functioning. The fact that chromosomally they were male, or that the gonads were testicular in structure was irrelevant to their psychologic healthiness as girls.

Some patients whose external body morphology and appearance was ambiguous looking and incongruous also had been assigned to and reared in the sex which contradicted their chromosomal and gonadal sex. Thus, there were 4 hyperadrenocortical females reared as boys; 2 females without the adrenal syndrome reared as boys; 3 males with well differentiated mullerian structures reared as girls; and 8 cryptorchid hypospadiac males reared as girls. Of these 17 individuals, 8 were rated as psychologically healthy. It is not possible to correlate the nonhealthy ratings of the other 9 with their chromosomal or gon-

TABLE VI

Psychologic Healthiness Ratings on 48 Teenage and Adult Patients

	Body morphology and appearance	
	Ambiguous	Unambiguous
Healthy	12	13
Mildly Nonhealthy	12	2
Mod. Nonhealthy	8	1

adal status. Their ratings reflect rather the disruptions of a reassignment of sex—4 cases—and, in two instances, congenital mental deficiency. In short, other things being equal, it proved quite possible for a patient to grow up psychologically healthy in the sex contradicted by chromosomes and gonads, and partially contradicted by genital appearance.

REASSIGNMENT OF SEX

Hermaphrodites who are assigned to one sex at birth and subsequently reassigned to the other sex are a particularly instructive group with reference to psychologic healthiness and nonhealthiness. There were 14 patients whose sex was reassigned, the youngest at one month of age, the oldest, on his own initiative, at sixteen years of age.

Ranged in order of age at the time of reassignment of sex, and rated for healthiness at least six months and at most twenty-one years later, these cases show clearly that the later in life a reassignment of sex, the greater the chance and the intensity of psychologic nonhealthiness.

Of 7 patients whose sex was reassigned between the ages of one and six months, 6 were rated healthy and 1 mildly nonhealthy.

Of 4 patients whose sex was reassigned between the ages of fifteen months and three years, 1 was rated healthy, 2 mildly nonhealthy and 1 moderately nonhealthy.

Of 3 patients whose sex was reassigned between the ages of four and sixteen years, all were rated moderately nonhealthy.

The symptoms of nonhealthiness in these patients were varied and diverse. The patients themselves did not connect their symptoms with their earlier change of sex, except for the thirty-seven year old man who himself had decided, at the age of sixteen, to cease living as a girl. Two other patients spoke about their change of sex, not from personal recall, but on the basis of subsequent hearsay. One, a boy of seventeen, had been changed at five years of age. The other, a girl of five, had been changed at five months of age, and subsequently was reminded by other children that she had formerly been a boy; on account of her clitoral enlargement, she was also teased about turning back into a boy.

Neighborhood ridicule about being a freak and a half boy was prominent in the life of another girl, not subjected to a reassignment of sex, who was rated moderately nonhealthy. Other patients encountered more subtle insinuations about their authentic masculinity or femininity, and elaborated their own grave doubts and misgivings as well.

All in all, the ridicule, insinuation or misgivings of other people, as well as the about-face of a reassignment of sex, appear to have been very fruitful antecedents and concomitants of psychologic nonhealthiness in hermaphrodites, especially after the period of early infancy.

VISIBLE SOMATIC AMBISEXUALITY

Some hermaphrodites reach the teenage or adulthood living in the sex partially contradicted by their genital morphology or secondary sexual characteristics, or both. One might expect that life would present these patients with quandaries and problems over and above the usual and that, consequently, a high proportion of them would be rated nonhealthy.

There were 32 teenage and adult patients who looked ambiguous in body morphology and appearance, and 16 who did not. Their ratings for psychologic healthiness were distributed as follows (Table VI).

Some of the ambiguous looking patients would, without doubt, have warranted a rating of nonhealthy irrespective of their hermaphroditism. Nonetheless, it still appears from Table VI that ambiguity of genital and secondary sexual development facilitates psychologic nonhealthiness. This finding is not surprising. The surprise is that so many ambiguous looking patients were able to grow up and achieve a rating of psychologic healthiness or of nonhealthiness of only mild degree.

HYPERADRENOCORTICAL PATIENTS TREATED WITH CORTISONE

So far in this presentation, it has become evident that hermaphrodites whose somatic ambisexuality does not publicize itself have a psychologic advantage over those for whom the reverse holds. Similarly, those patients whose incongruities and contradictions are corrected at an early age have an advantage over those whose treatment is delayed.

Hermaphroditic patients for whom corrective treatment, surgical or hormonal, is delayed until the late teens or older do not have their quandary automatically resolved in its entirety once surgical or hormonal corrections are effected. Psychologically, they are confronted with a program of readaptation to the demands and expectancies of life, and their readaptation may be prolonged and beset with difficulties. The syndrome of readaptation, as it may be called, was most clearly evident in patients whose corrective treatment did not get under way until they were well beyond the ordinary adolescent age. Owing to the recency of the discovery of cortisone for correcting hyperadrenocorticism

in female pseudohermaphrodites, it happens that women with this severely virilizing syndrome had lived longer with conspicuous hermaphroditic incongruities uncorrected than any other of the patients in our study.

There were 8 hyperadrenocortical patients, ranging in age from twenty-three to forty-nine, who did not receive cortisone until adulthood. Some had had adrenal surgery earlier in life, and some genital reconstructive surgery, but all had remained hormonally virilized to an extreme degree. All had been reared as girls, were living as women, and had no intention whatsoever about changing to live as a man. They were profoundly embarrassed by what they considered the affliction of virilism. They considered feminizing treatment highly desirable and looked forward to the onset of menstruation and breast growth, as well as to a redistribution of hair growth along feminine lines.

For all of their desire to be rid of the stigmata of virilism and to undergo the physiological changes of a female puberty, these women had, nonetheless, found some sort of adaptation to life as virilized, abnormal looking individuals. Only one of them had married. One other had led an active sex life with boyfriends. Another was engaged and planned to marry at some unspecified time in the distant future. Love affairs and sexual relationships were excluded from the adaptation made to life by the remaining five patients.

Psychologic impedances associated with delayed attainment of a normal physiologic female puberty were twofold. The first impedance appeared to be associated very specifically with, indeed to be an effect of, realignments of body metabolism and functioning during the first week of cortisone therapy. The initial cortisone (or hydrocortisone) dosage for adults was 100 mg. a day for approximately a week until urinary 17-ketosteroids were sufficiently suppressed, and then 75 mg. every third day. During the first week, patients reported divers subjective changes in feeling and perception, their reports coinciding with the onset of generalized edema and sodium retention.* One exceptionally articulate patient reported that she felt a vague and diffuse tiredness, weakness, depression and pessimistic gloom in which all of the tasks and problems of living seemed hopelessly magnified. Simultaneously, she felt a contradictory feeling of restlessness, as though sitting on the side of a volcano that might blow up. There was no accompanying thought content, but an urgent sense of responsibility to keep everything under control and to prevent an explosion. In addition to these two contradictory feeling states, the patient described an unpleasant somatic feeling of a bloated, over-full stomach and insatiable, ravenous hunger.

*The full clinical picture was discovered and investigated in three patients. It was not indubitably absent in any patients, but was probably overlooked in those treated earliest in the series. Edema and sodium retention appears to be lessened or absent when metacorten is used instead of cortisone or hydrocortisone, but feeling and mood changes are not necessarily eliminated.

All of these disturbing feelings disappeared after the new electrolyte balance was established and the cortisone dosage was lowered. In the meantime, however, the patient's psychologic distress was magnified by what she construed as contempt and disdain from the nursing and house staff when she reported the first changes of feeling. Subsequently, she emphasized how adversely she had been affected by the belief that her doctors thought she was a fraudulent neurotic and complaining hypochondriac. She also emphasized how greatly she had been restabilized when the psychiatrist listened seriously to her descriptions of her feelings and reassured her that her experiences were not unique and would be transient. Like several other patients, this woman was well enough informed, from the popular press, about ACTH and cortisone psychoses to be panicky lest she were losing her mind as a result of receiving cortisone.

It is remarkable, though so far unexplained, that juvenile and teenage patients have not shown any signs of these peculiar reactions to the initial week of cortisone treatment.

The younger patients were also exempt from what proved to be the second impedance associated with delayed attainment of normal female puberty, namely, the negotiation of adolescence alone, completely without the group enterprises and social encouragements of age mates. The more successfully the older women had come to terms with life as virilized individuals who could not expect to be attractive to men, the more difficult did they find the social and psychologic transition of adolescence after hormonal feminization and physiologic puberty began. Arrived anachronistically at a stage in life when their wildest romantic daydreams at last had a chance of coming true, these women found themselves awkward, inexpert and unself-assured at living the role of debutante, fiancée, lover or, perhaps, wife. So anachronistic an adolescence brought moody spells of depression and diverse bodily symptoms of severe anxiety in its train, four of these older women in particular having been so affected periodically.

Some of the older teenage girls also manifested similar signs of difficulty in coping with an anachronistic adolescence. By contrast, the preteenage girls, precocious in their virilism and also precocious in their feminizing response to cortisone, mixed socially with other adolescents somewhat older than themselves and negotiated the psychologic transition to adulthood with considerable facility, even if they had formerly been psychologically somewhat upset. Evidently, there are optimal growing periods for psychologic as well as somatic growth. Evidently, also, it is no easy matter to turn the clock back once an optimal period for psychologic growth and development has run its course.

SUMMARY

Ninety-four hermaphroditic patients, representing eight varieties of hermaphroditism, have been under comprehensive psychologic and psychiatric

study, and their psychologic healthiness has been appraised. On a four point rating scale, the 94 cases were distributed as follows: 63 healthy, 16 mildly nonhealthy, 14 moderately nonhealthy, 1 severely nonhealthy. The one severely nonhealthy patient was a congenital mental defective. Absence of psychosis, or rather lack of a high incidence of the so-called functional psychoses, is considered the most noteworthy finding of this study.

There was a marked tendency for mild and moderate nonhealthiness to show up as an excess of inhibitory and control functions of the personality. The symptoms included, among others, retardation of psychologic growth and personality development relative to IQ and life age; depressive moody spells; sullen and anxious bashfulness and shyness; and extreme but circumscribed diffidence and guardedness pertaining to sexual and romantic situations.

A rating of healthy was more common among infants and juveniles than among teenagers and adults, doubtless because the younger patients in our series had not experienced the impact of their hermaphroditic paradox with the same full force as the older patients had.

A rating of healthy was also more common among patients whose body morphology, irrespective of gonads and chromosomes, was unambiguous looking than among those whose sexual appearance was equivocal.

Patients whose sex of rearing was contradicted by chromosomal or gonadal sex were not necessarily destined to receive a nonhealthy rating. Reassignment of the sex of rearing after the early months of life was extremely conducive to subsequent psychologic nonhealthiness. Corrective surgical, hormonal or psychologic procedures were more beneficial if applied during infancy or childhood than later. Adaptation to a physiologic normalcy first induced during adulthood was seen to be a complex and difficult psychologic process, notably in adult hyperadrenocortical female pseudohermaphrodites feminized on cortisone therapy.

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ABSTRACTS OF PAPERS PRESENTED BEFORE THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

October 17, 1955

SOME PHYSIOLOGICAL EXPERIMENTS WITH A HISTOCHEMICAL METHOD FOR PROTEIN-BOUND SULFUR

ARNOLD M. SELIGMAN AND RUSSELL J. BARRNETT

A method for demonstrating protein-bound sulfhydryl groups was developed with the reagent 2,2′-dihydroxy-6,6′-dinaphthyl disulfide (1). It was shown that this method was specific for demonstrating sulfhydryl groups and that both disulfide and sulfhydryl groups could also be demonstrated after appropriate reduction of the disulfide groups in tissue sections (2). Depending upon the method of fixing tissue, various sulfur-containing proteins could be shown histochemically within cells.

Excretory enzymes were demonstrated in the apical portion of cells of the acini of the pancreas of the fasted rat after fixation in Zenker's fluid but not after fixation in alcohol-trichloroacetic acid and not after injection of pilocarpine (2).

Antidiuretic hormone was demonstrated in colloid-like structures of the posterior pituitary gland when fixed in Zenker's fluid. This material was depleted in dehydrated rats, reaccumulated on rehydration, and disappeared after stalk section (3).

Sulfur-containing protein was demonstrated in acidophilic cells of the anterior pituitary gland after fixation in Zenker's fluid. This protein, thought to be associated with ACTH and growth hormone was absent in hereditary dwarf mice and disappeared from normal mice after stress. The same results were reported on assay. Adrenalectomy resulted in increased staining and cortisone injection restored the picture to that of the normal mouse (4, 5).

Insulin was demonstrated in beta cells of the islets of Langerhans after fixation in Romeis fluid but not after alcohol-trichloroacetic acid fixation. The reaction was weaker after injecting insulin, infusing glucose solution or injecting alloxan. The reaction was greater after starvation, immediately after partial pancreatectomy and after injecting diethyl dithiocarbamate (6).

The work indicates the profitable use of specific histochemical methods, supplemented by information gained from *in vitro* analysis and physiological experiments, to determine the topographical localization of certain specific hormones.

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THE WORK OF BREATHING

ARTHUR B. OTIS

Breathing is a form of muscular exercise. The resting breathing of a normal individual requires metabolic energy equivalent to about 0.5 milliliters of oxygen per liter of ventila-

tion. The mechanical work done in displacing the lungs and chest and in moving respired gas is about 0.05 kilogram meters per liter of ventilation. The mechanical efficiency of breathing is about 5 per cent. In spite of this low efficiency, breathing ordinarily cools rather than warms the body, because the evaporative heat loss usually exceeds metabolic heat production.

For a given alveolar ventilation there is an optimal frequency of breathing in the sense that at that frequency a minimal amount of work is required. The optimal frequency is greater the smaller the dead space, the smaller the air flow resistance, the smaller the compliance of the chest and lung, and the greater the alveolar ventilation. Studies by Christie and his associates indicate that the body tends to select optimal frequencies for breathing in a variety of conditions of health and disease.

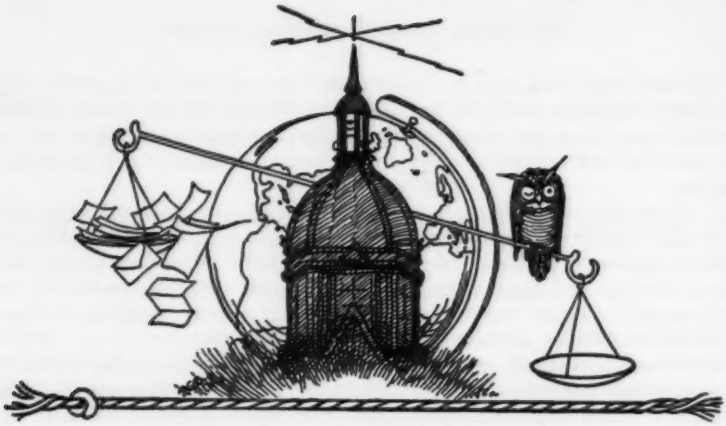
The unit cost of breathing is not constant but increases with increasing ventilation, so that at very high ventilations in normal individuals and at more moderate ventilations in individuals with obstructive pulmonary disease, the energy required for breathing becomes a considerable factor. Because of this increasing unit cost there is a point beyond which a further increase in ventilation will produce an increase rather than a decrease of the carbon dioxide tension of the body. In normal resting people this critical ventilation is probably about 70 liters per minute, but in individuals with obstructive respiratory disease the value may be much lower, as low as 12 liters per minute according to some measurements made in Cournand's laboratory. Thus, the diminished ventilatory response to carbon dioxide that occurs in obstructive respiratory disease may be thought of as a useful adaptation, in that it protects the body from doing useless or even detrimental work.

GENETICS OF THE ADRENOGENITAL SYNDROME

Barton Childs and Melvin M. Grumbach

A study was made of those aspects of data obtained on patients with virilizing adrenal hyperplasia pertaining to a possible genetic etiology. In the series studied there were 76 patients in 56 families. Statistical analysis by two methods indicated good agreement between the numbers of observed affected patients in the families and the numbers of affected which would be expected if the disease were due to an autosomal recessive gene. Though there was a heavy preponderance of affected females in the data, there was a strong suggestion that this preponderance is due to biases in ascertainment of cases, since when only secondary cases are considered the male/female sex ratio approached unity. A survey of the clinical variations among affected patients revealed homogeneity within, but heterogeneity between families. This suggests that if the disease is genetically determined at all, there may well be more than one gene involved, though the data do not indicate whether a system of multiple alleles, or genes at different loci might account for the different clinical pictures in the different families.

The nature of the biochemical lesion in the disease suggested some approaches to the detection of chemical characteristics in the parents similar to those found in the patients. If these could be found, the hypothesis of genetical etiology would be given a firmer foundation. Accordingly, 20 parents were stimulated with ACTH and urinary pregnanediol, 17-ketosteroids, and pregnanetriol were measured. As controls, 18 normal individuals were studied in the same way. Comparisons of the increments after stimulation of the various metabolites between parents and controls were then made. The increments of pregnanediol and 17-ketosteroids were negligible. The mean increment of pregnanetriol for the parents was suggestively higher than that of the controls, though not significantly so. In the aggregate there appears to be substantial evidence favoring the hypothesis of genetic etiology of virilizing adrenal hyperplasia.



BOOK REVIEWS

Sexual Precocity (American Lecture Series). By HUGH JOLLY. 276 pp., $6.75. Charles C Thomas, Springfield, Illinois.

This book is the latest in the American Lecture Series monographs. In physical characteristics it is a superb example of the excellence and pride of craftsmanship evident in books published by the Charles C Thomas Company.

The work was originally presented as the author's thesis for the degree of M.D. at the University of Cambridge. In this reviewer's opinion its appearance in book form at this time is not entirely justified. With the possible exception that some readers may find it a convenience to have the literature on the subject organized within the covers of a single book, the volume does not appear to add much to what has gone before.

The first half of the book is devoted to a general discussion of sexual precocity, its various causes and manifestations. Present-day knowledge is well summarized in a commendably succinct and readable manner. The usefulness of this section is enhanced by an extensive bibliography.

The second half of the book consists of a series of 69 abridged case reports of patients personally examined by the author. In half the cases the brief documentation is supplemented by photographic evidence. These case reports are effective examples of the case history method of teaching.

Included in the case studies are notes concerning the psychologic status and development of the patients and the inclusion of these observations is alleged to be a noteworthy feature of the monograph. It is true that there are occasions when claims of expertness from psychiatrists and psychologists can be overweening and even grandiose. It is also true that some psychiatric observations and judgments can equally well be made by the general pediatrician as the psychiatric specialist. There are, however, occasions when only the long, patient and skilled work of the psychiatric specialist will suffice. Psychologic study of sexual precocity is one of these occasions. The psychologic claims of this book are unfortunately overstretched to the breaking point; the psychologic data are much too meagre, anecdotal and uncomprehensively piecemeal. The author's statement (page 79), for example, that "female pseudohermaphrodites are in many instances male in mental outlook as well as in physique on account of the high concentration of circulating hormones . . ." is utterly conjectural and imprecise. Recent psychologic studies of patients with hermaphroditism have

demonstrated with clarity that gender role and outlook as boy or man, girl or woman, agrees with the sex of rearing and is not automatically or instinctively determined by hormones, chromosomes or gonads. The overall value of the book might have been enhanced by a closer collaboration with psychiatric colleagues, expert in medical psychology.

JOHN L. HAMPSON

Peptic Ulcer. Diagnosis and Treatment. By CLIFFORD J. BARBORKA AND E. CLINTON TEXTER, JR. 290 pp., $7.00. Little, Brown & Co., Boston, Mass.

This is a monograph on peptic ulcer written for the general practitioner. It deals in a straight forward and conventional manner with ulcer; etiology, pathogenesis, symptomatology, diagnosis, treatment, complications, etc. Although the authors state in the preface that "our discussion is constantly directed toward helping the practicing physician in his efforts to receive the full cooperation of his patient," much of the material is a summation of various technical data which do not directly relate to the stated objective. Much of the data is extremely interesting and it is worthwhile to have the information gathered together with ready references. The authors are not too discriminating and have in some instances included conflicting data without clarifying their own ideas on the subject. The indexing is not always accurate. A particularly effective part is the authors' treatment in a clearcut and quite sensible way of the discussion on practical psychotherapy of the ulcer patient. One wishes that this section could have been amplified. This is a practical manual for the practicing physician and perhaps the "ulcer" patient as well.

JOHN COLLINS HARVEY

Clinical Orthopaedics, No. 5. Edited by ANTHONY F. DEPALMA. 242 pp., $7.50 individual copies; $5.00 to sustaining members and subscribers. J. B. Lippincott Co., Philadelphia, Pa.

The fifth volume of Clinical Orthopaedics is devoted mainly to the problem of low back pain. There are fifteen articles presenting as many opinions. The authors agree that the price the human pays for having learned to walk on two legs instead of four, is a weak back. This universal agreement gives way to universal disagreement however in approaching the problem of treatment. From manipulation to surgery, all gradations of opinion are advocated.

Many small pearls of wisdom are dropped as the authors present their answers to the backache problem. An article devoted to back braces and supports was informative and interesting. About the only aspect of backache that did not receive its proper share of attention was the role of the psyche.

One is impressed by the uniform difference of opinion as to what constitutes the correct method of treatment. Despite this, the reported results are all good. The moral of this symposium may be that any reasonable treatment, carried to completion (and perhaps none at all) will in the course of time give satisfactory results.

A forum of this type is valuable in that it alerts the clinical orthopedist to the fact that there are many different ways of skinning a cat, and that there may even be a better method than the one he has used for many years.

With its line drawings, good x-ray reproduction, and clear printing, this volume is easy and interesting reading.

JESSE N. BORDEN

Proceedings of the Forum Sessions; Fortieth Clinical Congress of the American College of Surgeons. Atlantic City, N. J., November, 1954. Surgical Forum Committee: Harris B. Shumaker, Jr., Chairman, J. Garrott Allen, Bradford Cannon, Warren H. Cole,

Robert E. Gross, J. Albert Key, C. Hunter Shelden, Howard C. Taylor, Jr., Samuel A. Vest. 851 pp., $10.00. W. B. Saunders Co., Philadelphia, Pa.

Just as the Forum sessions are among the most eagerly attended at the annual meeting of the American College of Surgeons so will this volume be avidly read by those interested in surgical research. Projects are reported concisely by individual authors working in many and varied fields. Of particular value in this volume are the introductory comments by chairmen of the various sessions who attempt to place proper emphasis on particularly significant projects, obviously a difficult task in the evaluation of basic research.

This volume is of interest to those concerned with topics varying from steroid metabolism to cardiovascular surgery. It should be a source of pleasure to the reader who wishes to scan the field of surgical research and a must to anyone directly connected with this aspect of surgical practice.

HENRY T. BAHNSON

Pathology for the Surgeon, 7th Edition. By WILLIAM BOYD. 737 pp., $12.50. W. B. Saunders Co., Philadelphia, Pa.

The new edition of Dr. Boyd's surgical pathology textbook is entitled, *Pathology for the Surgeon*. As with all of Dr. Boyd's writings, this book is very readable. He has a flair for going directly to the essential points of the lesion he is describing and then clearly describing its pertinent features. While this book is essentially the product of Dr. Boyd's long experience in pathology, he has also incorporated many concepts from the recent literature.

In the chapter on carcinoma of the lung one is most impressed with his very sound and common-sense approach to the alleged increasing incidence of this disease and the role of various carcinogens in its etiology. This type of approach pervades the entire book.

While the trained pathologist probably will not use this book to any appreciable extent, it is entitled *Pathology for the Surgeon* and as such it is a very excellent book and a source of significant references for those wishing to study more exhaustive papers on the various lesions.

S. L. EVERSOLE

Connective Tissues. Transactions of the Fifth Conference, February 8, 9 and 10, 1954. Edited by Charles Ragan. 222 pp., $4.25. The Josiah Macy, Jr. Foundation, New York, N. Y.

This is the fifth and last of a series of Macy Conferences on connective tissues. Clearly the conferences were originally suggested by the relatively recent intensification of interest in acquired disorders of connective tissues and by the discovery of dramatic but poorly understood effects of adrenal steroids. The earlier conferences have been individually reviewed previously in the *Bulletin* (Bull. Johns Hopkins Hosp. 1952, **90:** 334; 1952, **90:** 453; 1953, **92:** 76; 1954, **94:** 286).

This is not the place to discuss in detail the advantages and shortcomings of the technique used in the conduct of the Macy Conferences. Suffice it to say that, although these get-togethers have doubtlessly been of great value to the participants, the "choppy", informal, and at times anarchistic character of the proceedings severely limits their usefulness to the reader of the recorded transactions. In the same general field the Ciba Symposia are much more useful in the published form since they combine the advantages of an orderly, uninterrupted, scientific survey of a particular aspect of a general topic with the healthy give-and-take of active discussion. The volume entitled *Nature and Structure of Collagen* (1953), edited by J. T. Randall, although also the published proceedings of a symposium, is also a much more useful synthesis of the multidisciplinary studies of one important element of connective tissue.

Lack of any evident order in the planning of the conferences makes it difficult to obtain a grasp of the various ramifications of the field such as one might expect from perusing these volumes. Some of the contributions, although in themselves presenting highly significant and interesting work, are of questionable pertinence and, on the other hand, certain significant areas are left untouched.

For the benefit of those who may wish to know some of the specific topics covered in the symposia, the following are listed together with the name of the contributor and year of presentation: Polysaccharides (Karl Meyer, 1950); the elastic fiber (Lansing, 1951); connective tissue staining (Lillie, 1952); electron microscopy (Wyckoff, 1952); the nature of reticulin (Robb-Smith, 1952); fibrinoid degeneration (Bennett, 1950); hormonal effects on connective tissue (Asboe-Hansen, 1954); Ragan, (1950); tissue culture studies (Porter, 1951).

VICTOR A. MCKUSICK

BOOKS RECEIVED FOR REVIEW

Bailliere's Pocket Book of Ward Information (Heimann & Wilson), 8th edition revised. By MARJORIE HOUGHTON. 179 pp., $2.00. Bailliere, Tindall and Cox, London, England. Distributed by The Williams & Wilkins Co., Baltimore, Md.

Basic Surgical Skills. A Manual with Appropriate Exercises. By ROBERT TAUBER. 75 pp., $3.75. W. B. Saunders Co., Philadelphia, Pa.

Cardiac Diagnosis. A Physiologic Approach. By ROBERT F. RUSHMER. 447 pp., $11.50. W. B. Saunders Co., Philadelphia, Pa.

Corticotropin: Its Pharmacologic Effects in Man and Practical Therapeutic Utilization. By GORDON B. MYERS AND WILLIAM Q. WOLFSON. 80 pp., $1.75. Wayne University Press, Detroit, Michigan.

The Diagnosis and Treatment of Haemophilia and its Related Conditions. Medical Research Council Memorandum No. 32. By R. G. MACFARLANE AND ROSEMARY BIGGS. 23 pp., 2s. 6d. net. Her Majesty's Stationery Office, London, England.

Essentials of Chemistry, 6th edition. By GRETCHEN O. LUROS. 544 pp., $4.75. J. B. Lippincott Co., Philadelphia, Pa.

Group Processes. Transactions of the First Conference September, 1954. Edited by BERTRAM SCHAFFNER. 334 pp., $5.50. The Josiah Macy, Jr. Foundation, New York, N. Y.

Henry Ford Hospital International Symposium on Cardiovascular Surgery. Studies in Physiology, Diagnosis and Techniques. Edited by CONRAD R. LAM. 543 pp., $12.75. W. B. Saunders Co., Philadelphia, Pa.

Indian Year-Book of Ophthalmology, 1954. Edited by VAMAN D. SATHAYE. 232 pp. Sangam Press, Poona, India.

Introduction to Virology. By GILBERT DALLDORF. 102 pp., $3.50. Charles C Thomas, Springfield, Illinois.

Mental Hygiene in Public Health, 2nd edition. By PAUL V. LEMKAU. 486 pp., $8.00. McGraw-Hill Series in Health Science. The Blakiston Division, McGraw-Hill Book Co., New York, N. Y.

Nursing Practice and the Law, 2nd edition. By MILTON J. LESNIK AND BERNICE E. ANDERSON. 400 pp., $6.00. J. B. Lippincott Co., Philadelphia, Pa.

Preventive Medicine in World War II. Vol. II. Environmental Hygiene. Editor in Chief COL. JOHN BOYD COATES, JR. Editor for Preventive Medicine, EBBE CURTIS HOFF. 404 pp., $3.50. U. S. Government Printing Office, Washington, D. C.

Prevention of Heart Disease and Cancer. (Bioclimatology and Etiology). By J. E. BITTNER. 57 pp. Bittner Research Foundation, Yakima, Washington.